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1	0
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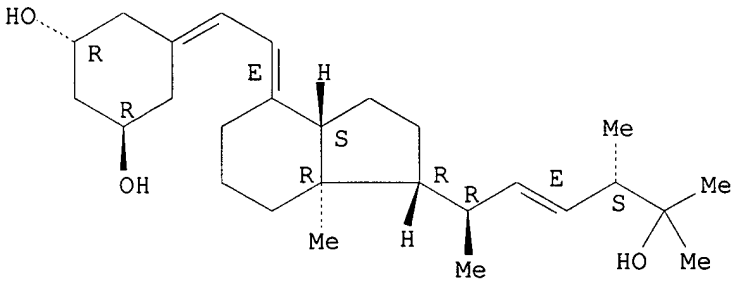
L10 ANSWER 1 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **131918-61-1** REGISTRY
CN 19-Nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol, (1.alpha.,3.beta.,7E,22E)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Paricalcitol
CN Zemplar
FS STEREOSEARCH
MF C27 H44 O3
SR CA
LC STN Files: ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PHAR, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.

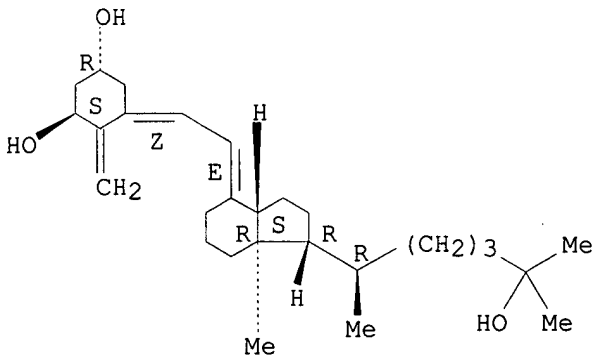


35 REFERENCES IN FILE CA (1967 TO DATE)
35 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L10 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **32222-06-3** REGISTRY
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,25-Dihydroxycholecalciferol
CN 1,25-Dihydroxyvitamin D
CN 1,25-Dihydroxyvitamin D3
CN 1.alpha.,25-(OH)2D3
CN 1.alpha.,25-Dihydroxycholecalciferol
CN 1.alpha.,25-Dihydroxyvitamin D3
CN Calcijex
CN Calcitriol
CN Ro 21-5535
CN Rocaltrol
CN Soltriol
CN Topitriol
FS STEREOSEARCH
DR 125338-24-1
MF C27 H44 O3
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS*, TOXLINE, TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO

(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
Double bond geometry as shown.



8576 REFERENCES IN FILE CA (1967 TO DATE)
239 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8586 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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FILE 'HOME' ENTERED AT 12:00:44 ON 08 AUG 2001

=> fil capl
=> s delgado-Herrera, l?/au
L1            3 DELGADO-HERRERA, L?/AU

=> d ti tot

L1   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2001 ACS
TI   Sevoflurane: approaching the ideal inhalational anesthetic a
     pharmacologic, pharmacoeconomic, and clinical review

L1   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2001 ACS
TI   The effects of sevoflurane on serum creatinine and blood urea nitrogen
     concentrations: A retrospective, twenty-two-center, comparative evaluation
     of renal function in adult surgical patients

L1   ANSWER 3 OF 3  CAPLUS  COPYRIGHT 2001 ACS
TI   Inhalation toxicity study of a haloalkene degradant of sevoflurane,
     compound A (PIFE), in Sprague-Dawley rats


=> s zager, r?/au
L2           86 ZAGER, R?/AU

=> s mershimer, p?/au
L3            0 MERSHIMER, P?/AU

=> s l2 and l1
L4            0 L2 AND L1

=> s vitamin d and l2
         122703 VITAMIN
          32946 VITAMINS
         136874 VITAMIN
                (VITAMIN OR VITAMINS)
        1718417 D
          16709 VITAMIN D
                (VITAMIN(W)D)
L5            1 VITAMIN D AND L2

=> d

L5   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2001 ACS
AN   1999:395866  CAPLUS
DN   131:194784
TI   Calcitriol directly sensitizes renal tubular cells to ATP-depletion- and
     iron-mediated attack
AU   Zager, Richard A.
CS   Fred Hutchinson Cancer Research Center and the University of Washington,
     Seattle, WA, 98109-1024, USA
SO   Am. J. Pathol. (1999), 154(6), 1899-1909
     CODEN: AJPAA4; ISSN: 0002-9440
PB   American Society for Investigative Pathology
DT   Journal
LA   English
RE.CNT  53
RE
(1) Abe, E; Proc Natl Acad Sci 1981, V78, P4990 CAPLUS
(2) Anderson, R; J Am Soc Nephrol 1998, V9, P773 CAPLUS
(3) Baran, D; Endocrinology 1988, V122, P930 CAPLUS
(4) Baran, D; J Bone Mineral Res 1988, V3, P593 CAPLUS
(5) Baran, D; J Clin Invest 1986, V77, P1622 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT


=> fil reg

=> s 1,25-dihydroxyvitamin D2
           440 1,25
           118 DIHYDROXYVITAMIN
         29299 D2
```

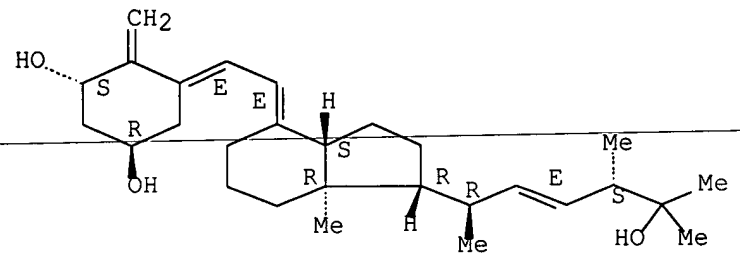
```
L6            3 1,25-DIHYDROXYVITAMIN D2
                (1,25(W)DIHYDROXYVITAMIN(W)D2)

=> s 1,25-dihydroxy vitamin D2
           440 1,25
        285762 DIHYDROXY
          1307 VITAMIN
             3 VITAMINS
          1309 VITAMIN
                (VITAMIN OR VITAMINS)
         29299 D2
L7            3 1,25-DIHYDROXY VITAMIN D2
                (1,25(W)DIHYDROXY(W)VITAMIN(W)D2)

=> d

L7   ANSWER 1 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   73837-25-9  REGISTRY
CN   9,10-Secoergosta-5,7,10(19),22-tetraene-1,3,25-triol,
     (1.alpha.,3.beta.,5E,7E,22E)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   5,6-trans-1,25-Dihydroxyergocalciferol
CN   5,6-trans-1,25-Dihydroxyvitamin D2
FS   STEREOSEARCH
MF   C28 H44 O3
LC   STN Files:   BEILSTEIN*, CA, CAPLUS, TOXLIT, USPATFULL
       (*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.
```

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              13 REFERENCES IN FILE CA (1967 TO DATE)
              13 REFERENCES IN FILE CAPLUS (1967 TO DATE)


=> d 2-3

L7   ANSWER 2 OF 3  REGISTRY  COPYRIGHT 2001 ACS
RN   60133-18-8  REGISTRY
CN   9,10-Secoergosta-5,7,10(19),22-tetraene-1,3,25-triol,
     (1.alpha.,3.beta.,5Z,7E,22E)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   1,25-Dihydroxycalciferol
CN   1,25-Dihydroxyergocalciferol
CN   1,25-Dihydroxyvitamin D2
CN   1.alpha.,25-Dihydroxycalciferol
CN   1.alpha.,25-Dihydroxyergocalciferol
CN   1.alpha.,25-Dihydroxyvitamin D2
CN   Ercalcitriol
CN   Ro 17-6218
FS   STEREOSEARCH
MF   C28 H44 O3
LC   STN Files:   AGRICOLA, BEILSTEIN*, BIOBUSINESS, BIOSIS, CA, CAPLUS,
       CASREACT, CHEMCATS, DDFU, DRUGU, TOXLIT, USPATFULL
         (*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.
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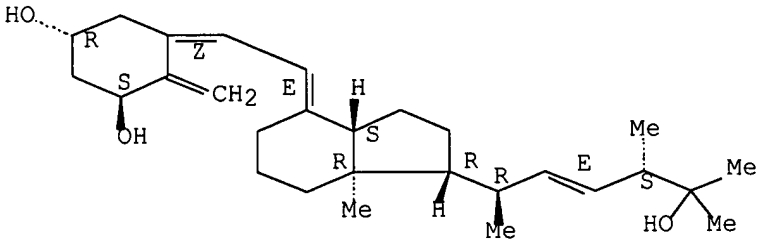
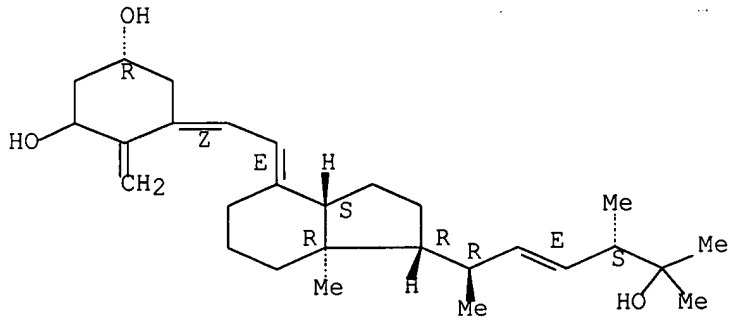


112 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
112 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L7 ANSWER 3 OF 3 REGISTRY COPYRIGHT 2001 ACS
RN 55248-15-2 REGISTRY
CN 9,10-Secoergosta-5,7,10(19),22-tetraene-1,3,25-triol, (3.beta.,5Z,7E,22E)-(9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,25-Dihydroxyergocalciferol
CN **1,25-Dihydroxyvitamin D2**
FS STEREOSEARCH
MF C28 H44 O3
LC STN Files: AGRICOLA, BEILSTEIN*, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, EMBASE, IFICDB, IFIPAT, IFIUDB, MEDLINE, TOXLINE, TOXLIT, USPATFULL
(*File contains numerically searchable property data)

Absolute stereochemistry.
Double bond geometry as shown.



57 REFERENCES IN FILE CA (1967 TO DATE)
57 REFERENCES IN FILE CAPLUS (1967 TO DATE)

=> s 1,25-dihydroxy 19-nor vitamin D2
440 1,25
285762 DIHYDROXY
207512 19
117716 NOR
67 NORS
117716 NOR
(NOR OR NORS)
1307 VITAMIN
3 VITAMINS
1309 VITAMIN
(VITAMIN OR VITAMINS)
29299 D2

```
L8            0 1,25-DIHYDROXY 19-NOR VITAMIN D2
                (1,25(W)DIHYDROXY(W)19(W)NOR(W)VITAMIN(W)D2)

=> s 1,25-dihydroxy and vitamin D2 and 19-nor
            440 1,25
         285762 DIHYDROXY
             82 1,25-DIHYDROXY
                (1,25(W)DIHYDROXY)
           1307 VITAMIN
              3 VITAMINS
           1309 VITAMIN
                (VITAMIN OR VITAMINS)
          29299 D2
             69 VITAMIN D2
                (VITAMIN(W)D2)
         207512 19
         117716 NOR
             67 NORS
         117716 NOR
                (NOR OR NORS)
          14987 19-NOR
                (19(W)NOR)
L9            0 1,25-DIHYDROXY AND VITAMIN D2 AND 19-NOR

=> fil caplus
=> sel l5 1 rn
E1 THROUGH E6 ASSIGNED

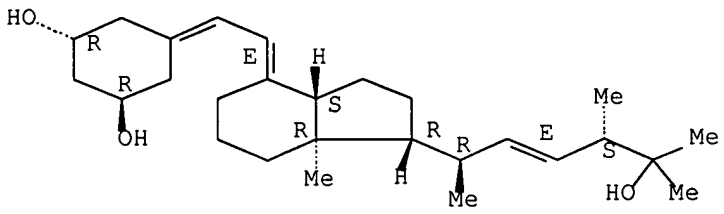
=> fil reg

=> s e1-e6
              1 131918-61-1/BI
                (131918-61-1/RN)
              1 32222-06-3/BI
                (32222-06-3/RN)
              1 56-65-5/BI
                (56-65-5/RN)
              1 58-64-0/BI
                (58-64-0/RN)
              1 7439-89-6/BI
                (7439-89-6/RN)
              1 7722-84-1/BI
                (7722-84-1/RN)
L10           6 (131918-61-1/BI OR 32222-06-3/BI OR 56-65-5/BI OR 58-64-0/BI OR
                7439-89-6/BI OR 7722-84-1/BI)

=> d tot

L10  ANSWER 1 OF 6  REGISTRY  COPYRIGHT 2001 ACS
RN   131918-61-1  REGISTRY
CN   19-Nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol,
     (1.alpha.,3.beta.,7E,22E)- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   Paricalcitol
CN   Zemplar
FS   STEREOSEARCH
MF   C27 H44 O3
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CANCERLIT, CAPLUS, DDFU,
       DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE,
       MRCK*, PHAR, PROMT, SYNTHLINE, TOXLINE, TOXLIT, USPATFULL
         (*File contains numerically searchable property data)

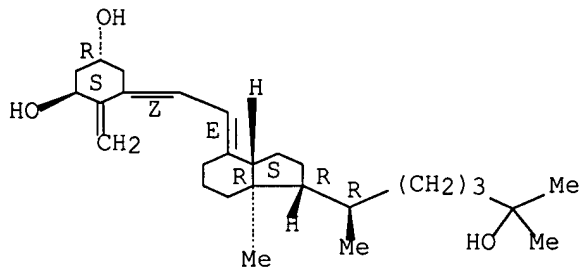
Absolute stereochemistry.
Double bond geometry as shown.
```



35 REFERENCES IN FILE CA (1967 TO DATE)
35 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L10 ANSWER 2 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **32222-06-3** REGISTRY
CN 9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1.alpha.,3.beta.,5Z,7E)-
(9CI) (CA INDEX NAME)
OTHER NAMES:
CN 1,25-Dihydroxycholecalciferol
CN 1,25-Dihydroxyvitamin D
CN 1,25-Dihydroxyvitamin D3
CN 1.alpha.,25-(OH)2D3
CN 1.alpha.,25-Dihydroxycholecalciferol
CN 1.alpha.,25-Dihydroxyvitamin D3
CN Calcijex
CN Calcitriol
CN Ro 21-5535
CN Rocaltrol
CN Soltriol
CN Topitriol
FS STEREOSEARCH
DR 125338-24-1
MF C27 H44 O3
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*,
BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAPLUS, CASREACT,
CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU,
DIOGENES, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY,
IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PROMT, RTECS*, TOXLINE,
TOXLIT, USAN, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: EINECS**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.
Double bond geometry as shown.



8576 REFERENCES IN FILE CA (1967 TO DATE)
239 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
8586 REFERENCES IN FILE CAPLUS (1967 TO DATE)

L10 ANSWER 3 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **7722-84-1** REGISTRY
CN Hydrogen peroxide (H2O2) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:

CN Hydrogen peroxide (8CI)
OTHER NAMES:
CN Albone
CN Albone 35
CN Albone DS
CN Baquashock
CN CIX
CN Hipox
CN Hybrite
CN Hydrogen dioxide
CN Inhibine
CN Metrokur
CN Odosat D
CN Oxydol
CN Oxyfull
CN Oxysept I
CN Perhydrol
CN Perone
CN Peroxaan
CN Peroxclean
CN Select Bleach
CN Superoxol
CN T-Stuff
FS 3D CONCORD
DR 8007-30-5, 66554-50-5, 37355-84-3, 218625-72-0
MF H2 O2
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CHEMSAFE, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, GMELIN*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PDLCOM*, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TRCTHERMO*, TULSA, ULIDAT, USAN, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

HO—OH

58136 REFERENCES IN FILE CA (1967 TO DATE)
565 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
58247 REFERENCES IN FILE CAPLUS (1967 TO DATE)
2 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L10 ANSWER 4 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **7439-89-6** REGISTRY
CN Iron (7CI, 8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 300A
CN 3ZhP
CN A 227
CN Ancor B
CN Ancor EN 80/150
CN Armco iron
CN Atomel 300M200
CN Atomel 500M
CN Atomet 28
CN Atomiron 44MR
CN Atomiron 5M
CN Atomiron AFP 25
CN Atomiron AFP 5
CN ATW 230
CN ATW 432
CN Carbonyl iron
CN CM (iron)
CN Copy Powder CS 105-175
CN DH
CN Diseases (animal), iron overload

CN Diseases, iron overload
CN DSP 128B
CN DSP 135
CN DSP 135C
CN DSP 138
CN EF 1000
CN EF 250
CN EFV
CN EFV 200/300
CN EFV 250
CN EFV 250/400
CN EO 5A
CN F 60
CN F 60 (metal)
CN Ferrovac E
CN FT 3
CN FT 3 (element)
CN GS 6
CN HF 2
CN HF 2 (element)
CN HL (iron)
CN Hoeganaes ATW 230
CN Hoeganaes EH
CN HS (iron)
CN HS 4849
CN Iron element
CN Iron fulleride (FeC20)
CN ISP 3700
CN ISP-CIP-R 1470
CN KG 200
ADDITIONAL NAMES NOT AVAILABLE IN THIS FORMAT - Use FCN, FIDE, or ALL for DISPLAY
DR 8011-79-8, 8053-60-9, 129048-51-7, 73135-38-3, 70884-35-4, 39344-71-3, 195161-83-2, 199281-22-6
MF Fe
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, APILIT, APILIT2, APIPAT, APIPAT2, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, CSNB, DDFU, DETHERM*, DIOGENES, DIPPR*, DRUGU, EMBASE, HSDB*, IFICDB, IFIPAT, IFIUDB, IMSDIRECTORY, IPA, MEDLINE, MRCK*, MSDS-OHS, NIOSHTIC, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, TULSA, ULIDAT, USPATFULL, VETU, VTB
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

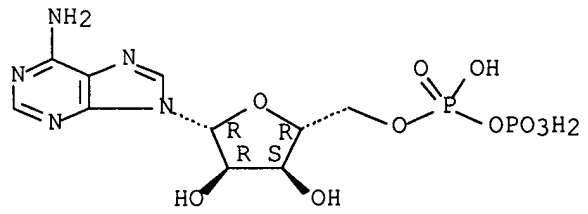
Fe

274425 REFERENCES IN FILE CA (1967 TO DATE)
16759 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
274735 REFERENCES IN FILE CAPLUS (1967 TO DATE)
1 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L10 ANSWER 5 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **58-64-0** REGISTRY
CN Adenosine 5'-(trihydrogen diphosphate) (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Adenosine 5'-(trihydrogen pyrophosphate) (8CI)
CN Adenosine diphosphate (6CI)
OTHER NAMES:
CN .alpha.-ADP
CN 5'-ADP
CN Adenosine 5'-diphosphate
CN Adenosine 5'-diphosphoric acid
CN Adenosine 5'-pyrophosphate
CN Adenosine 5'-pyrophosphoric acid
CN Adenosine pyrophosphate
CN Adenosine, 5'-(trihydrogen diphosphate)

CN ADP
CN ADP (nucleotide)
FS STEREOSEARCH
DR 84412-16-8
MF C10 H15 N5 O10 P2
CI COM
LC STN Files: AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGU, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NIOSHTIC, PIRA, PROMT, RTECS*, TOXLINE, TOXLIT, USPATFULL, VETU
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.

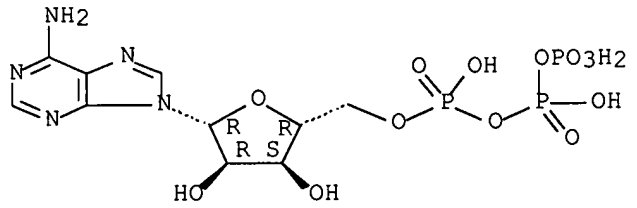


19748 REFERENCES IN FILE CA (1967 TO DATE)
449 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
19769 REFERENCES IN FILE CAPLUS (1967 TO DATE)
22 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

L10 ANSWER 6 OF 6 REGISTRY COPYRIGHT 2001 ACS
RN **56-65-5** REGISTRY
CN Adenosine 5'-(tetrahydrogen triphosphate) (8CI, 9CI) (CA INDEX NAME)
OTHER NAMES:
CN 5'-ATP
CN Adenosine 5'-triphosphate
CN Adenosine 5'-triphosphoric acid
CN Adenosine triphosphate
CN Adenosine, 5'-(tetrahydrogen triphosphate)
CN Adenylpyrophosphoric acid
CN Adephos
CN Adetol
CN Adynol
CN Atipi
CN ATP
CN ATP (nucleotide)
CN Atriphos
CN Cardenosine
CN Fosfobion
CN Glucobasin
CN Myotriphos
CN Phosphobion
CN Striadyne
CN Triadenyl
CN Triphosphaden
CN Triphosphoric acid adenosine ester
FS STEREOSEARCH
DR 10168-83-9, 16488-07-6, 51569-41-6, 71800-44-7, 84412-18-0
MF C10 H16 N5 O13 P3
CI COM
LC STN Files: ADISINSIGHT, AGRICOLA, AIDSLINE, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CABA, CANCERLIT, CAOLD, CAPLUS, CASREACT, CEN, CHEMCATS, CHEMLIST, CIN, CSCHEM, DDFU, DETHERM*, DRUGNL, DRUGU, DRUGUPDATES, EMBASE, GMELIN*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, NAPRALERT, NIOSHTIC, PHAR, PIRA, PROMT, RTECS*, SPECINFO, TOXLINE, TOXLIT, TULSA, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**

(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.



58014 REFERENCES IN FILE CA (1967 TO DATE)
1077 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
58079 REFERENCES IN FILE CAPLUS (1967 TO DATE)
19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

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=> sel chem 1,2 l10
E7 THROUGH E23 ASSIGNED

=> fil hcaplus

=> s e7-e23
             4 CALCIJEX/BI
          2435 CALCITRIOL/BI
             4 CALCITRIOLS/BI
          2436 CALCITRIOL/BI
                 ((CALCITRIOL OR CALCITRIOLS)/BI)
            15 PARICALCITOL/BI
         25514 "RO"/BI
          4833 "ROS"/BI
         30321 "RO"/BI
                 (("RO" OR "ROS")/BI)
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            11 "RO 21-5535"/BI
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            17 SOLTRIOL/BI
             1 TOPITRIOL/BI
             2 ZEMPLAR/BI
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           203 "OHS"/BI
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          9380 "DIHYDROXYVITAMIN"/BI
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         27789 "D3"/BI
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             0 125338-24-1/BI
            35 131918-61-1/BI
          8586 32222-06-3/BI
L11      11643 (CALCIJEX/BI OR CALCITRIOL/BI OR PARICALCITOL/BI OR "RO 21-5535"
                /BI OR ROCALTROL/BI OR SOLTRIOL/BI OR TOPITRIOL/BI OR ZEMPLAR/BI
                 OR "1.ALPHA.,25-(OH)2D3"/BI OR "1.ALPHA.,25-DIHYDROXYCHOLECALCI
                FEROL"/BI OR "1.ALPHA.,25-DIHYDROXYVITAMIN D3"/BI OR "1,25-DIHYD
                ROXYCHOLECALCIFEROL"/BI OR "1,25-DIHYDROXYVITAMIN D"/BI OR "1,25
                -DIHYDROXYVITAMIN D3"/BI OR 125338-24-1/BI OR 131918-61-1/BI OR
                32222-06-3/BI)

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            35 131918-61-1
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                 (131918-61-1 (NOTL) 131918-61-1D )
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          8441 32222-06-3/RN
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L12       8457 131918-61-1/RN OR  32222-06-3/RN

=> s l11 or l12
L13      11643 L11 OR L12

=> s hypocalc?
L14       3433 HYPOCALC?

=> s l13 and l14
L15        387 L13 AND L14

=> s critic? or icu or intensive care
         88393 CRITIC?
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```
        291110 CRIT
            10 CRITS
        291116 CRIT
                 (CRIT OR CRITS)
        333376 CRITIC?
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           426 ICU
            48 ICUS
           450 ICU
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         30275 INTENSIVE
            13 INTENSIVES
         30284 INTENSIVE
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         23437 CARE
            95 CARES
         23520 CARE
                 (CARE OR CARES)
          1535 INTENSIVE CARE
                 (INTENSIVE(W)CARE)
L16     334889 CRITIC? OR ICU OR INTENSIVE CARE

=> s l15 and l16
L17          5 L15 AND L16

=> d ibib abs kwic

L17  ANSWER 1 OF 5  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        2000:154820  HCAPLUS
DOCUMENT NUMBER:         132:278020
TITLE:                   RANK is the intrinsic hematopoietic cell surface
                         receptor that controls osteoclastogenesis and
                         regulation of bone mass and calcium metabolism
AUTHOR(S):               Li, Ji; Sarosi, Ildiko; Yan, Xiao-Qiang; Morony, Sean;
                         Capparelli, Casey; Tan, Hong-Lin; McCabe, Susan;
                         Elliott, Robin; Scully, Sheila; Van, Gwyneth; Kaufman,
                         Stephen; Juan, Shao-Chieh; Sun, Yu; Tarpley, John;
                         Martin, Laura; Christensen, Kathleen; McCabe, James;
                         Kostenuik, Paul; Hsu, Hailing; Fletcher, Frederick;
                         Dunstan, Colin R.; Lacey, David L.; Boyle, William J.
CORPORATE SOURCE:        Department of Cell Biology, Amgen Inc., Thousand Oaks,
                         CA, 91320, USA
SOURCE:                  Proc. Natl. Acad. Sci. U. S. A. (2000), 97(4),
                         1566-1571
                         CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER:               National Academy of Sciences
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   We have generated RANK (receptor activator of NF-.kappa.B) nullizygous
     mice to det. the mol. genetic interactions between osteoprotegerin,
     osteoprotegerin ligand, and RANK during bone resorption and remodeling
     processes.  RANK-/- mice lack osteoclasts and have a profound defect in
     bone resorption and remodeling and in the development of the cartilaginous
     growth plates of endochondral bone.  The osteopetrosis obsd. in these mice
     can be reversed by transplantation of bone marrow from rag1-/-
     (recombinase activating gene 1) mice, indicating that RANK-/- mice have an
     intrinsic defect in osteoclast function.  Calciotropic hormones and
     proresorptive cytokines that are known to induce bone resorption in mice
     and human were administered to RANK-/- mice without inducing
     hypercalcemia, although tumor necrosis factor .alpha. treatment leads to
     the rare appearance of osteoclast-like cells near the site of injection.
     Osteoclastogenesis can be initiated in RANK-/- mice by transfer of the
     RANK cDNA back into hematopoietic precursors, suggesting a means to
     critically evaluate RANK structural features required for bone
     resorption.  Together these data indicate that RANK is the intrinsic cell
     surface determinant that mediates osteoprotegerin ligand effects on bone
     resorption and remodeling as well as the physiol. and pathol. effects of
     calciotropic hormones and proresorptive cytokines.
REFERENCE COUNT:         29
REFERENCE(S):            (1) Anderson, D; Nature (London) 1997, V390, P175
                             HCAPLUS
                         (2) Boyce, B; Endocrinology 1989, V125, P1142 HCAPLUS
                         (3) Bucay, N; Genes Dev 1998, V12, P1260 HCAPLUS
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(4) Chung, U; Proc Natl Acad Sci USA 1998, V95, P13030
HCAPLUS
(5) Darnay, B; J Biol Chem 1999, V274, P7724 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB We have generated RANK (receptor activator of NF-.kappa.B) nullizygous mice to det. the mol. genetic interactions between osteoprotegerin, osteoprotegerin ligand, and RANK during bone resorption and remodeling processes. RANK-/- mice lack osteoclasts and have a profound defect in bone resorption and remodeling and in the development of the cartilaginous growth plates of endochondral bone. The osteopetrosis obsd. in these mice can be reversed by transplantation of bone marrow from rag1-/- (recombinase activating gene 1) mice, indicating that RANK-/- mice have an intrinsic defect in osteoclast function. Calciotropic hormones and proresorptive cytokines that are known to induce bone resorption in mice and human were administered to RANK-/- mice without inducing hypercalcemia, although tumor necrosis factor .alpha. treatment leads to the rare appearance of osteoclast-like cells near the site of injection. Osteoclastogenesis can be initiated in RANK-/- mice by transfer of the RANK cDNA back into hematopoietic precursors, suggesting a means to **critically** evaluate RANK structural features required for bone resorption. Together these data indicate that RANK is the intrinsic cell surface determinant that mediates osteoprotegerin ligand effects on bone resorption and remodeling as well as the physiol. and pathol. effects of calciotropic hormones and proresorptive cytokines.

ST RANK receptor activator NFkappaB osteoclast differentiation hematopoietic precursor; osteoprotegerin ligand RANK osteoclastogenesis bone resorption osteopetrosis osteoporosis; calcium phosphate **hypocalcemia** hypophosphatemia RANK parathyroid hormone; interleukin TNF humoral hypercalcemic factor dihydroxy vitamin D3 RANK; cytokine receptor RANK hyperparathyroidism osteoclastogenesis

IT 7440-70-2, Calcium, biological studies
RL: BOC (Biological occurrence); BPR (Biological process); BIOL (Biological study); OCCU (Occurrence); PROC (Process)
(**hypocalcemia**; intrinsic hematopoietic cell surface receptor RANK in control of osteoprotegerin ligand-induced osteoclastogenesis and in regulation of bone mass and calcium metab.)

IT **32222-06-3**, 1.alpha.,25-Dihydroxy vitamin D3 103370-86-1, Humoral hypercalcemic factor
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(intrinsic hematopoietic cell surface receptor RANK in control of osteoprotegerin ligand-induced osteoclastogenesis and in regulation of bone mass and calcium metab. in relation to)

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=> s l13 (s) l14
PROXIMITY OPERATOR LEVEL NOT CONSISTENT WITH
FIELD CODE - 'AND' OPERATOR ASSUMED 'L13 (S) L14'
L18        387 L13 (S) L14

=> s l18 and thu/rl
        386705 THU/RL
L19         28 L18 AND THU/RL

=> focus
PROCESSING COMPLETED FOR L19
L20          28 FOCUS L19 1-

=> d ibib abs 1-5

L20  ANSWER 1 OF 28  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        1998:403415  HCAPLUS
DOCUMENT NUMBER:         129:183655
TITLE:                   Therapy of hypocalcemia from renal failure
                         with 26,26,26,27,27,27-hexafluoro-1,
                         25-dihydroxyvitamin D
AUTHOR(S):               Kumeda, Yasuro; Inaba, Masaaki
CORPORATE SOURCE:        Second. Dep. Intern. Med., Osaka City, Japan
SOURCE:                  Clin. Calcium (1998), 8(5), 653-657
                         CODEN: CLCCEJ; ISSN: 0917-5857
PUBLISHER:               Iyaku Janarusha
DOCUMENT TYPE:           Journal; General Review
LANGUAGE:                Japanese
```

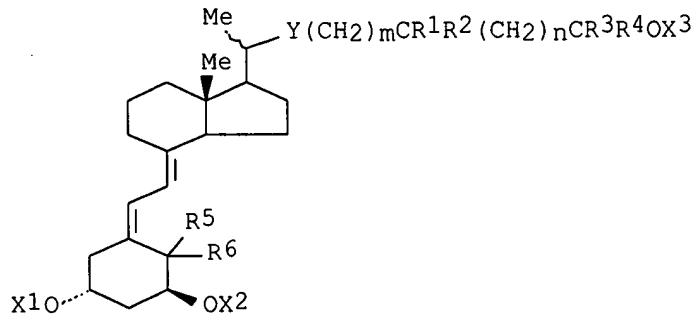
AB A review, with 11 refs., of the chem., action mechanism, and clin. pharmacol. of 26,26,26,27,27,27-hexafluoro-**1,25-dihydroxyvitamin D** for treatment of **hypocalcemia** from renal failure.

L20 ANSWER 2 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:332363 HCAPLUS
DOCUMENT NUMBER: 126:308791
TITLE: Preparation of **calcitriol** derivatives as in vivo vitamin D activity modulators
INVENTOR(S): Deluca, Hector F.; Schnoes, Heinrich K.; Cai, Zu Yun; Phelps, Mary E.; Smith, Connie M.
PATENT ASSIGNEE(S): Wisconsin Alumni Research Foundation, USA; Deluca, Hector F.; Schnoes, Heinrich K.; Cai, Zu Yun; Phelps, Mary E.; Smith, Connie M.
SOURCE: PCT Int. Appl., 44 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9711053	A1	19970327	WO 1996-US15184	19960920
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM				
US 5952317	A	19990914	US 1995-531403	19950921
CA 2229316	AA	19970327	CA 1996-2229316	19960920
AU 9672426	A1	19970409	AU 1996-72426	19960920
AU 717238	B2	20000323		
JP 11511475	T2	19991005	JP 1996-512945	19960920
EP 1021401	A1	20000726	EP 1996-933853	19960920
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
NO 9801282	A	19980522	NO 1998-1282	19980320
US 5976784	A	19991102	US 1998-43509	19980522

PRIORITY APPLN. INFO.: US 1995-531403 A 19950921
US 1995-531867 A 19950921
WO 1996-US15184 W 19960920

OTHER SOURCE(S): MARPAT 126:308791
GI



I

AB Modified vitamin D compds. I [R1, R2, R3, R4 = H, (substituted) OH, F, CF3, alkyl; R1R2 = oxo, alkylidene, etc.; R5, R6 = H; R5R6 = CH2; X1, X2, X3 = H, acyl, hydrocarbyloxycarbonyl group; m, n = 0-5; Y = O, CH2O, CH=CH, C.tplbond.C] are prepd. to regulate the in vivo release of the active form of vitamin D. Thus, **1.alpha.,25-dihydroxyvitamin D3** was esterified with glacial

acetic acid to give **1.alpha.,25-dihydroxyvitamin D3** 1,3,25-triacetate. The serum calcium response of **1.alpha.,25-dihydroxyvitamin D3** 1,3,25-triacetate over 48 h showed a delayed response until 12 to 18 h post-dose, peaking at 24 h. The time of conversion of the modified compd. to its active form, such as **calcitriol**, can be regulated to thus provide controlled release of the compd. in vivo over time, by changing or modifying the hydrolyzable groups.

L20 ANSWER 3 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:732806 HCAPLUS
DOCUMENT NUMBER: 126:85038
TITLE: Vitamin D receptors from patients with resistance to **1,25-dihydroxyvitamin D3**: point mutations confer reduced transactivation in response to ligand and impaired interaction with the retinoid X receptor heterodimeric partner
AUTHOR(S): Whitfield, G. Kerr; Selznick, Sanford H.; Haussler, Carol A.; Hsieh, Jui-Cheng; Galligan, Michael A.; Jurutka, Peter W.; Thompson, Paul D.; Lee, Stanley M.; Zerwekh, Joseph E.; Haussler, Mark R.
CORPORATE SOURCE: Dep. Biochemistry, Univ. Arizona College Medicine, Tucson, AZ, 85724, USA
SOURCE: Mol. Endocrinol. (1996), 10(12), 1617-1631
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hereditary **hypocalcemic** vitamin D-resistant rickets is attributable to defects in the nuclear receptor for **1,25-dihydroxyvitamin D3** [1,25-(OH)2D3]. Two novel point mutations (I314S and R391C) identified in the hormone-binding domain of the human vitamin D receptor (VDR) from patients with hereditary **hypocalcemic** vitamin D-resistant rickets confer the receptor with sharply reduced 1,25-(OH)2D3-dependent transactivation. These natural mutations, esp. R391C, also lead to a second specific consequence, namely impaired heterodimeric interaction with retinoid X receptor (RXR). While the transactivation ability of the I314S mutant can be largely restored by providing excess 1,25-(OH)2D3, R391 activity is more effectively restored with exogenous RXR. These observations are reflected also in the clin. course of each patient: the patient bearing the I314S mutation showed a nearly complete cure with pharmacol. doses of a vitamin D deriv., whereas the patient bearing R391C responded only partially to such therapy. Further tests with patient fibroblasts and transfected cells show that the activity of the I314S VDR mutant is augmented somewhat by added RXR, while transactivation by the R391C mutant is best cor. by RXR in the presence of excess hormone. Thus, the effects of hormone vs. RXR in bolstering these mutant VDRs, such that they mediate efficient transactivation, are not entirely separable. The unique properties of these genetically altered receptors establish a new subclass of natural human VDR mutants that illustrate, in vivo, the importance of both 1,25-(OH)2D3 binding and heterodimerization with RXR in VDR action.

L20 ANSWER 4 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:666143 HCAPLUS
DOCUMENT NUMBER: 125:318765
TITLE: Changes in periparturient plasma parathyroid hormone and **1,25-dihydroxyvitamin D** levels in cows with milk fever history
AUTHOR(S): Yamagishi, Norio; Ooizumi, Yoshiaki; Sato, Reeko; Naito, Yoshihisa
CORPORATE SOURCE: Fac. Agriculture, Iwate Univ., Morioka, 020, Japan
SOURCE: Nippon Juishikai Zasshi (1996), 49(10), 724-728
CODEN: NIPJAV; ISSN: 0446-6454
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB Periparturient plasma calcium (Ca), parathyroid hormone (PTH) and **1,25-dihydroxyvitamin D** [1,25-(OH)2D] levels were evaluated in 8 cows with milk fever history (historied cases) and 5 cows without the history (controls). The lowest plasma Ca level was recorded around delivery in both historied cases and

controls. Decreases levels of plasma Ca were lower in the 5 historied cases than those of the controls, and one of historied cases developed milk fever, in which the decrease of plasma Ca levels persisted in spite of the immediate elevation of plasma PTH and 1,25-(OH)2D values. Although this **hypocalcemia** recovered after Ca therapy, plasma Ca value decreased again at 2 days after the clin. onset in assocn. with an addnl. greater elevation of plasma 1,25-(OH)2D levels.

L20 ANSWER 5 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:257890 HCAPLUS
DOCUMENT NUMBER: 132:264514
TITLE: Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications
AUTHOR(S): Rao, D. Sudhaker; Honasoge, M.; Divine, George W.; Phillips, Evelyn R.; Lee, Min W.; Ansari, Mohammed R.; Talpos, Gary B.; Parfitt, A. Michael
CORPORATE SOURCE: Division of Bone and Mineral Metabolism, Department of Medicine, Henry Ford Health System, Detroit, MI, 48202, USA
SOURCE: J. Clin. Endocrinol. Metab. (2000), 85(3), 1054-1058
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In primary hyperparathyroidism, adenoma size is a major determinant of disease severity and manner of presentation, but the reason for the large variation in size (>100-fold) is unknown. One factor could be the level of vitamin D nutrition, because in India, where vitamin D deficiency is endemic, adenomas are larger and the disease more severe than in the U.S. Accordingly, we detd. the relationship between vitamin D nutrition, as measured by serum levels of 25-hydroxyvitamin D (25OHD), and parathyroid gland wt., expressed on a logarithmic scale, in 148 U.S. patients with primary hyperparathyroidism. A significant inverse relationship was found between log gland wt. as dependent variable and serum 25OHD as independent variable ($r = -0.365$; $P < 0.0001$). The only other influence on gland wt. was a weak inverse correlation with age. Log gland wt. as an independent variable was significantly related to adjusted calcium, PTH, and alk. phosphatase (AP) as dependent variables. In 51 patients with serum 25OHD levels less than 15 ng/mL, gland wt., PTH, AP, and adjusted calcium were each significantly higher than in 97 patients with 25OHD levels of 15 ng/mL or more, but **1,25-dihydroxyvitamin D** levels were similarly increased in both groups. In the former group the response of adjusted calcium to PTH was blunted, and the response of AP was enhanced, based on significant differences in regression slopes ($P = 0.0004$ and 0.0022, resp.). Suboptimal vitamin D nutrition stimulates parathyroid adenoma growth by a mechanism unrelated to **hypocalcemia** or **1,25-dihydroxyvitamin D** deficiency and reduces the calcemia response to PTH, so that a higher PTH level and more parathyroid cells are needed to raise the patient's serum calcium to the level corresponding to the increased set-point that is characteristic of the disease. Improved vitamin D nutrition in the population is partly, perhaps largely, responsible for the historical changes in disease severity and manner of presentation that have occurred over the last 50 yr.
REFERENCE COUNT: 36
REFERENCE(S): (2) Clements, M; Clin Endocrinol (Oxf) 1992, V37, P17 HCAPLUS
(3) Cooke, N; Vitamin D binding protein 1997, P87 HCAPLUS
(16) Mawer, E; Clin Sci Mol Med 1975, V48, P349 HCAPLUS
(20) Parfitt, A; Clin Sci Mol Med 1975, V49, P91 HCAPLUS
(22) Parfitt, A; J Clin Endocrinol Metab 1998, V83, P863 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs 6-28

L20 ANSWER 6 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:257897 HCAPLUS
DOCUMENT NUMBER: 133:29199

TITLE: Changes in parameters of bone and mineral metabolism during therapy for hyperthyroidism

AUTHOR(S): Pantazi, Helen; Papapetrou, Peter D.
CORPORATE SOURCE: Second Division of Endocrinology and Metabolism, Alexandra Hospital, Athens, 115 28, Greece

SOURCE: J. Clin. Endocrinol. Metab. (2000), 85(3), 1099-1106
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hyperthyroid patients have high bone turnover and neg. calcium and phosphorus balance often assocd. with mild osteopenia. Early during antithyroid treatment bone turnover decreases, the mineral balance is converted to pos., and sometimes **hypocalcemia** occurs. The aim of this investigation was to study the mechanisms of the changes in some parameters of bone and mineral metab. after treatment of thyrotoxicosis. Thirteen newly diagnosed patients with Graves' disease (seven postmenopausal women, four premenopausal women, and two men) were studied longitudinally, every 6 wk, for 1 yr after commencing antithyroid treatment with methimazole. Mean serum calcium and phosphorus were both slightly above the normal mean at week 0 and decreased significantly (by 10% and 24%, resp.) during treatment. Fasting urinary calcium was 236.+-.4 (mean .+-. SEM) mg/g creatinine, and the fractional excretion of Ca was 2.0.+-.0.33% before treatment; both fell significantly to min. of 61.+-.20 mg/g and 0.6.+-.0.16%, resp. Urinary phosphorus was 282.+-.60 mg/g creatinine, and the fractional excretion of phosphorus was 3.3.+-.0.6% before treatment; both increased significantly to 452.+-.40 mg/g and 8.4.+-.1.0%, resp., during treatment. The z-scores were calcd. from the mean and SD of the resp. control groups. The z-score of urinary N-telopeptides of type I collagen (U.NTx) was 9.3.+-.1.3 at week 0 and declined exponentially, but failed to normalize after 1 yr of antithyroid treatment. The serum alk. phosphatase (ALP) z-score was initially 2.2.+-.0.2, increased to 6.0.+-.1.0 at week 6, and declined slowly there after to 1.0.+-.1.1 at week 54. The serum osteocalcin (OC) z-score showed a temporal pattern similar to that of ALP. It was initially 2.2.+-.0.2, increased to 4.0.+-.0.6 at week 6, and later declined slowly to 0.7.+-.0.5 at week 54. The failure of the markers of bone turnover to normalize after 1 yr of therapy indicates an on-going high rate of bone turnover despite the attained euthyroidism. The uncoupling index (UI = z-score of U.NTx minus z-score of OC) was 7.1.+-.1.2 before treatment, indicating unbalanced bone turnover in favor of bone resorption, and fell close to zero at week 30 of treatment. Pretreatment plasma PTH was suppressed slightly to 2.17.+-.0.47 pmol/L and rose significantly during treatment, reaching a plateau of 5.27.+-.0.78 at week 12. In all postmenopausal women PTH increased above the upper limit of normal (6.84 pmol/L). Pretreatment serum 25-hydroxyvitamin D was normal and remained unchanged during treatment, whereas **1,25-dihydroxyvitamin D** was initially subnormal and rose to normal level after treatment. There was a significant pos. linear correlation between PTH and U.NTx after week 12. PTH was also significantly correlated with ALP, but not with OC. ALP and OC were significantly correlated. A significant pos. correlation was found between T3 and U.NTx, and a neg. correlation was found between T3 and each of the formation markers (ALP and OC) over the 0- to 12-wk interval. The latter correlations and the very high pretreatment UI indicate some inhibitory effect of the high thyroid hormone levels on the osteoblasts. The marked and sustained elevation of PTH, more pronounced in the postmenopausal women, during the first year of treatment of hyperthyroidism seems to play a pivotal role in maintaining a relatively high rate of bone turnover despite euthyroidism, and in the conservation of calcium by reducing renal calcium excretion and increasing calcium absorption (via **1,25-dihydroxyvitamin D**). It may also account in part for the addnl. rise of the bone formation markers by an anabolic effect on the osteoblasts. Endogenous PTH may be important in the restoration of bone mineral d. of treated hyperthyroid patients.

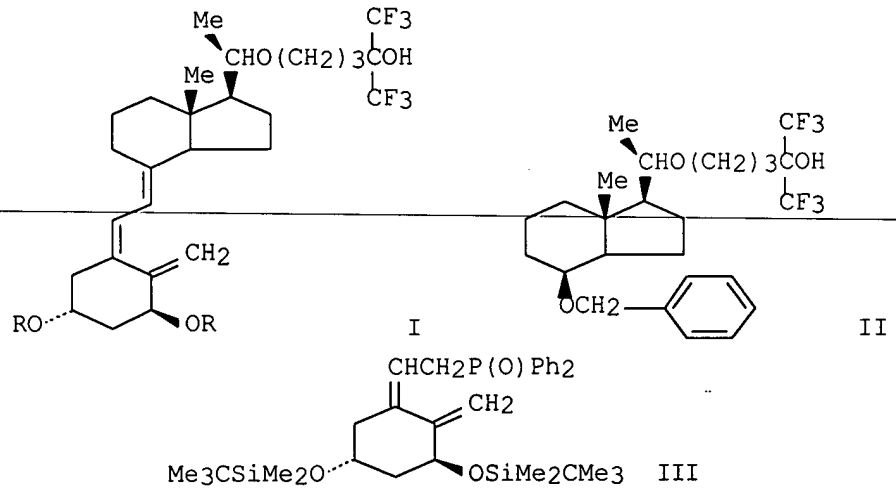
REFERENCE COUNT: 27
REFERENCE(S):
(1) Abu, E; Bone 1997, V21, P137 HCAPLUS
(2) Brown, E; The parathyroids Basic and clinical concepts 1994, P15 HCAPLUS
(3) Calvo, M; Endocr Rev 1996, V17, P333 HCAPLUS
(4) Cook, P; Q J Med 1959, V28, P505 HCAPLUS
(5) Cooper, D; Ann Intern Med 1979, V90, P164 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 7 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:87748 HCAPLUS
DOCUMENT NUMBER: 124:176621
TITLE: Preparation of fluorine-containing vitamin D3 analogs as neoplasm inhibitors
INVENTOR(S): Ikegawa, Nobuo; Kawai, Makoto; Kobayashi, Yoshiro; Izeki, Katsuhiko; Unten, Sakikazu
PATENT ASSIGNEE(S): Daikin Ind Ltd, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 07304732	A2	19951121	JP 1994-96151	19940510
JP 2850751	B2	19990127		

OTHER SOURCE(S): MARPAT 124:176621
GI



AB The title analogs I (R = H, OH-protective group) are claimed. I show low hypercalcemic effect and high differentiating effect on tumor cells. A THF soln. of bicyclo[4.3.0]nonane deriv. II (prepn. given) was treated with a reaction mixt. of phosphine oxide III and BuLi in THF to give 100% I (R = SiMe2CMe3), which in MeOH was treated with ion exchange resin under stirring at room temp. for 19 h to give 95% I (R = H) (IV). Hypercalcemic effect of IV on exptl. **hypocalcemic** rats was 0.1-0.2, vs. 1 for **1.alpha.,25-dihydroxyvitamin D3** (V). Differentiating effect of IV on human leukemia HL-60 was 11.0, vs. 1 for V.

L20 ANSWER 8 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:518790 HCAPLUS
DOCUMENT NUMBER: 129:225984
TITLE: Calreticulin inhibits vitamin D's action on the PTH gene in vitro and may prevent vitamin D's effect in vivo in **hypocalcemic** rats
AUTHOR(S): Sela-Brown, Alin; Russell, John; Koszewski, Nicholas J.; Michalak, Marek; Naveh-Many, Tally; Silver, Justin
CORPORATE SOURCE: Minerva Center for Calcium and Bone Metabolism

(A.S-B., T.N-M, J.S.) Nephrology Services, Hadassah University Hospital and Hebrew University Medical School, Jerusalem, 91120, Israel
SOURCE: Mol. Endocrinol. (1998), 12(8), 1193-1200
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **1,25-Dihydroxyvitamin D3** [1,25-(OH)2D3] and PTH both act to increase serum calcium. In addn., 1,25-(OH)2D3 decreases PTH gene transcription, which is relevant both to the physiol. of calcium homeostasis and to the management of the secondary hyperparathyroidism of patients with chronic renal failure. In chronic **hypocalcemia** there is secondary hyperparathyroidism with increased levels of PTH mRNA and serum PTH despite markedly increased levels of 1,25-(OH)2D3. We have studied the role of calreticulin in this resistance to 1,25-(OH)2D3. Weanling rats fed a low-calcium diet were **hypocalcemic** and had increased PTH mRNA levels despite high serum 1,25-(OH)2D3 levels. 1,25-(OH)2D3 given by continuous minipump infusion to normal rats led to the expected decrease in PTH mRNA. The **hypocalcemic** rats had an increased concn. of calreticulin in the nuclear fraction of their parathyroids, but not in other tissues. Gel shift assays showed that a purified vitamin D receptor and retinoid X receptor-.beta. bound to the PTH promoter's chicken and rat vitamin D response element (VDRE), and this binding was inhibited by added pure calreticulin. Transfection studies with a PTH VDRE-chloramphenicol acetyltransferase (CAT) construct showed that 1,25-(OH)2D3 decreased CAT transcription. Contransfection of PTH VDRE-CAT with a calreticulin expression vector in the sense orientation prevented the transcriptional effect of 1,25-(OH)2D3, but a calreticulin vector in the antisense orientation had no effect. These results show that calreticulin prevents the binding of vitamin D receptor-retinoid X receptor-.beta. to the PTH VDRE in gel retardation assays and prevents the transcriptional effect of 1,25-(OH)2D3 on the PTH gene. This is the first report of calreticulin inhibiting a down-regulatory function of a sterol hormone and may help explain the refractoriness of the secondary hyperparathyroidism of many chronic renal failure patients to 1,25-(OH)2D3.

L20 ANSWER 9 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:125827 HCAPLUS
DOCUMENT NUMBER: 126:156003
TITLE: Calcium metabolism in **hypocalcemic** cows with myocardial lesion
AUTHOR(S): Yamagishi, Norio; Naito, Yoshihisa
CORPORATE SOURCE: Department of Veterinary Internal Medicine, Faculty of Agriculture, Iwate University, Iwate, 020, Japan
SOURCE: J. Vet. Med. Sci. (1997), 59(1), 71-73
CODEN: JVMSEQ; ISSN: 0916-7250
PUBLISHER: Japanese Society of Veterinary Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper deals with blood levels of calcium (Ca), inorg. phosphorus, parathyroid hormone and **1,25-dihydroxyvitamin D** in 6 cows treated for milk fever. Four of the cows stood within 1 day after Ca therapy, whereas 2 other cases showed an unsatisfactory response to Ca therapy and did not rise. The necropsy revealed microscopic necrotic myocardial lesions scattered in the heart of these 2 unrecovered cows. The degree of **hypocalcemia** and hypophosphatemia were similar in the 6 cows. However, the recovery from hypophosphatemia was markedly delayed in the cows with an unsatisfactory response.

L20 ANSWER 10 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:75420 HCAPLUS
DOCUMENT NUMBER: 128:201198
TITLE: A calcimimetic agent acutely suppresses parathyroid hormone levels in patients with chronic renal failure
AUTHOR(S): Antonsen, John E.; Sherrard, Donald J.; Andress, Dennis L.
CORPORATE SOURCE: Department of Medicine, Veterans Affairs Medical Center and University of Washington, Seattle, WA, USA
SOURCE: Kidney Int. (1998), 53(1), 223-227
CODEN: KDYIA5; ISSN: 0085-2538

PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The control of hyperparathyroidism in patients with chronic renal failure continues to be a problem, particularly when parathyroid hormone (PTH) suppression becomes refractory to **calcitriol** activation of parathyroid cell **1,25-dihydroxyvitamin D** receptors. To evaluate whether parathyroid cell calcium receptor activation may be useful in suppressing PTH levels, we tested the safety and effectiveness of a novel calcimimetic agent in dialysis patients with hyperparathyroidism. In a prospective, dose finding study, the calcimimetic agent, NPS R-568, was administered orally to seven patients at the start of a hemodialysis session and again 24 h later. Plasma PTH, calcitonin and ionized calcium levels were measured over a 48 h period and patients were obsd. for adverse events. Plasma PTH levels fell abruptly in all patients after a single dose of the compd., with the max. suppression occurring within one to two hours after its administration. Following the administration of low doses (40 or 80 mg), the suppressed PTH levels rose to baseline values over 48 h, whereas in patients who received high doses (120 or 200 mg) the mean PTH level remained 51% below baseline. Plasma calcitonin increased after the administration of both low and high doses (peak effect within 4 to 6 h), with levels always returning to baseline by 48 h. There were no episodes of **hypocalcemia** and no adverse effects were reported. We conclude that the activation of parathyroid cell calcium receptors by a novel calcimimetic compd. is safe and effective in acutely suppressing PTH secretion in dialysis patients with hyperparathyroidism. Whether concomitant stimulation of calcitonin secretion will provide added beneficial effects on bone remodeling remains to be detd. in long-term studies.

L20 ANSWER 11 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:609175 HCAPLUS
DOCUMENT NUMBER: 131:223775
TITLE: Effect of **calcitriol** and age on recovery from **hypocalcemia** in hemodialysis patients
AUTHOR(S): Borrego, Maria J.; Martin-Malo, Alejandro; Almaden, Yolanda; Rodriguez, Mariano; Aljama, Pedro; Felsenfeld, Arnold J.
CORPORATE SOURCE: Department of Nephrology and the Unit of Investigation, Hospital Reina Sofia, Cordoba, 14004, Spain
SOURCE: Am. J. Kidney Dis. (1999), 34(3), 456-463
CODEN: AJKDDP; ISSN: 0272-6386
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Calcitriol** is used to treat hyperparathyroidism in hemodialysis patients. **Calcitriol** treatment, either through a redn. in parathyroid hormone (PTH) levels or direct effect on bone, decreases the osteoblast and osteoclast surface and bone formation rate. Our study of 13 hemodialysis patients was designed to evaluate whether **calcitriol** treatment changed the rate of spontaneous recovery from **hypocalcemia** induced by a low-calcium dialysis. **Calcitriol** treatment decreased basal PTH levels from 614.+-.84 to 327.+-.102 pg/mL ($P < 0.001$) and maximal PTH levels from 1,282.+-.157 to 789.+-.161 pg/mL ($P < 0.001$), but the rate of serum ionized calcium recovery from **hypocalcemia** did not change. When the 13 patients were sepd. based on the median age of 64 yr, the predialysis serum ionized calcium level was less in the younger (group I, 44.+-.6 yr; n = 6) than older (group II, 68.+-.1 yr; n = 7) patients (1.05.+-.0.03 v 1.22.+-.0.03 mmol/L, resp.; $P < 0.01$) despite similar basal (group I, 595.+-.122 pg/mL v group II, 629.+-.96 pg/mL) and maximal (group I, 1,114.+-.299 pg/mL v group II, 1,425.+-.141 pg/mL) PTH levels. Before **calcitriol** treatment, the rate of serum ionized calcium recovery from induced **hypocalcemia** was greater ($P < 0.05$) for similar PTH levels in the older than younger patients. After **calcitriol** treatment, despite a similar redn. in PTH levels, the rate of calcium recovery increased ($P < 0.05$) in the younger patients but did not change in the older patients. We also obsd. that toward the end of the low-calcium hemodialysis, PTH values decreased even though serum ionized calcium level continued to decline when the rate of calcium redn. slowed. In addn., hysteresis, defined as a lower PTH value during the recovery from

hypocalcemia than during the induction of **hypocalcemia** for the same serum calcium concn., was present during the spontaneous recovery from **hypocalcemia**. In conclusion, in the hemodialysis patient: (1) age appeared to affect the bone response to PTH and **calcitriol** treatment, (2) the PTH response to **hypocalcemia** was affected by a deceleration in the rate of calcium decrease, and (3) hysteresis of the PTH response to **hypocalcemia** occurred during the spontaneous recovery from **hypocalcemia**.

REFERENCE COUNT: 31
REFERENCE(S):
(3) Brent, G; J Clin Endocrinol Metab 1988, V67, P944 HCAPLUS
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(7) Cosman, F; J Bone Miner Res 1997, V12, P958 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 12 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:664009 HCAPLUS
DOCUMENT NUMBER: 130:60826
TITLE: Sustained reduction in urinary calcium during long-term treatment with slow release neutral potassium phosphate in absorptive hypercalciuria
AUTHOR(S): Heller, Howard J.; Reza-Albarran, Alfredo A.; Breslau, Neil A.; Pak, Charles Y. C.
CORPORATE SOURCE: Center for Mineral Metabolism and Clinical Research, University of Texas Southwestern Medical Center, Dallas, TX, 75235-8885, USA
SOURCE: J. Urol. (Baltimore) (1998), 159(5), 1451-1456
CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We tested whether UroPhos-K, a new slow release neutral form of potassium phosphate (155 mg. phosphate, 8 mEq. potassium per tablet) in a dose of 4 tablets twice daily would produce a sustained **hypocalciuric** response and maintain bone mass in patients with absorptive hypercalciuria, a major cause of nephrolithiasis characterized by excessive intestinal calcium absorption accompanied in some patients by excessive bone loss. A total of 25 patients with absorptive hypercalciuria were studied in a 4-yr, prospective, open trial with UroPhos-K at yearly intervals during a 4-day inpatient physiol. study with a const. metabolic diet contg. 400 mg. calcium, 100 mEq. sodium and 800 mg. phosphate daily. Treatment with UroPhos-K caused a sustained, marked redn. in urinary calcium (264 to 181 mg. daily). Fractional 47calcium absorption decreased modestly (74.0 to 64.6%) commensurate with a redn. in serum **1,25-dihydroxyvitamin D** (42 to 34 pg./mL.). Intact parathyroid hormone increased within the normal range (30 to 42 pg./mL.). Bone mineral d. was stable at the lumbar spine, femoral neck and distal third of the radius. UroPhos-K may provide a long-term alternative for hypercalciuric patients in whom thiazide therapy fails.

REFERENCE COUNT: 21
REFERENCE(S):
(2) Breslau, N; J Bone Min Res 1995, V10, P394 HCAPLUS
(7) Kivirikko, K; Anal Biochem 1967, V19, P249 HCAPLUS
(8) Lau, K; J Lab Clin Med 1982, V99, P317 HCAPLUS
(10) Nicar, M; J Urol 1984, V131, P430 HCAPLUS
(16) Rowe, J; J Gerontol 1976, V31, P155 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 13 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:453195 HCAPLUS
DOCUMENT NUMBER: 125:132219
TITLE: Effect of calcium-channel blockers on calcium-phosphate metabolism in patients with end-stage renal disease
AUTHOR(S): Lippuner, K.; Zehnder, H. -J.; Casez, J. P.; Takkinen, R.; Descoeudres, C.; Jaeger, Ph.
CORPORATE SOURCE: Policlinic Medicine, University Hospital, Bern,

CH-3010, Switz.
SOURCE: Nephrol., Dial., Transplant. (1996), 11(1), 70-74
CODEN: NDTREA; ISSN: 0931-0509
DOCUMENT TYPE: Journal
LANGUAGE: English

AB After EDTA-induced **hypocalcemia**, healthy volunteers treated with diltiazem display more severe hyperparathyroidism than subjects on felodipine studied under identical conditions. Therefore patients with end-stage renal disease (ESRD) and severe secondary hyperparathyroidism might be particularly sensitive to this side-effect. To test this hypothesis, seven patients with ESRD on chronic hemodialysis (3 women and 4 men) with serum levels of intact PTH ranging from 204 to 675 pg/mL were studied both before and during the first 180 min of hemodialysis against a dialyzate with low calcium concn. (0.75 mmol/l, n=6 and 1 mmol/l, n=1) under the following three exptl. conditions: control, felodipine (10 mg/day) and diltiazem (120 mg b.i.d.). At onset of dialysis, plasma phosphorus level was higher on diltiazem (2.03.+-.0.08 mM) than on felodipine (1.64.+-.0.10, P <0.02), and on the latter it was lower than in control condition (1.88.+-.0.16, P <0.02). As a probable consequence, blood ionized calcium concn. was lower on diltiazem (1.14 mM.+-.0.02, mean .+-. SEM) than on felodipine (1.2.+-.0.03, P <0.05) or in control condition (1.17.+-.0.01, NS). There was a trend for intact PTH to be higher on diltiazem (324.+-.47 pg/mL) than on felodipine (246.+-.55) or in control condition (305.+-.49) and **1,25-dihydroxyvitamin D** was higher indeed on diltiazem (6.70.+-.0.92 pg/mL) than on felodipine (4.75.+-.0.91, P <0.02) or control (3.87.+-.0.62, P <0.05). Area under the curve PTH over the first 60 min of dialysis was higher by 16.+-.7% on diltiazem than on felodipine (P <0.05). While on diltiazem rather than on felodipine, patients with ESRD display higher plasma phosphorus levels, and slightly aggravate the degree of severity of hyperparathyroidism recorded during hemodialysis against low-calcium dialyzate. The long-term effect of this new observation remains to be evaluated.

L20 ANSWER 14 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:713477 HCAPLUS
DOCUMENT NUMBER: 131:322832
TITLE: Preparation of active vitamin D derivatives and their uses as drugs
INVENTOR(S): Tachibana, Yoji
PATENT ASSIGNEE(S): Nisshin Flour Milling Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11310569	A2	19991109	JP 1998-118580	19980428

OTHER SOURCE(S): MARPAT 131:322832
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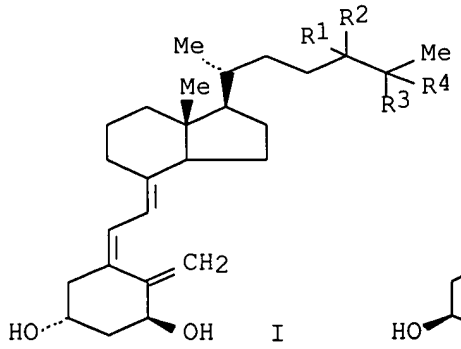

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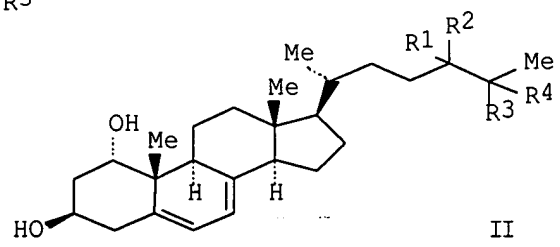

II

AB The derivs. I (1 of R1-R4 = COR5, 1 of the others = OH, and the other 2 = H, C1-4 alkyl; R5 = OH, C1-4 alkoxy), useful as bone mineral improvers, differentiation inducers, and immunomodulators, are prepd. by UV irradn. of the precursors II (R1-R5 = same as in I) and then thermal isomerization of the resulting product. I show less **hypocalcemic** effect and are useful for treatment of osteoporosis, cancer, autoimmune diseases, GVHD, etc. (25R)-1.alpha.,3.beta.,25-trihydroxyergosta-5,7-diene-26-carboxylic acid Me ester (200 mg, prepn. given) was dissolved in THF and the soln. was irradiated with UV for 10 min and then heated under reflux for 1 h to give 21 mg (25R)-1.alpha.,3.beta.,25-trihydroxy-9,10-secoergosta-5Z,7E,10(19)-triene-26-carboxylic acid Me ester. This compd. showed differentiation-inducing activity on HL 60 leukemia cells comparable to that of **1,25-dihydroxyvitamin D3** (III) although the vitamin D receptor-binding capacity was less than III. Pharmaceutical formulations of I were also given.

L20 ANSWER 15 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:428040 HCAPLUS
DOCUMENT NUMBER: 122:204895
TITLE: Effects of avicatonin (synthetic [Asu1,7] chicken calcitonin) on bone resorption - avicatonin inhibits generation of multinucleated osteoclast-like cells and their activities -
AUTHOR(S): Hakeda, Yoshiyuki; Kurihara, Noriyoshi; Arai, Yasuhiro; Kumegawa, Masayoshi
CORPORATE SOURCE: Sch. Dentistry, Meikai Univ., Sakado, 350-02, Japan
SOURCE: Yakuri to Chiryo (1994), 22(Suppl. 13), S3281-S3288
CODEN: YACHDS; ISSN: 0386-3603
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Biol. activities of avicatonin (synthetic[Asu1,7]chicken calcitonin) were investigated in vivo and in vitro. Avicatonin at a dose of 5 U/kg body wt. in mice rapidly decreased serum Ca level, as well as elcatonin did. The **hypocalcemic** effect lasted for at least 4 h. In organ culture of mouse calvariae prelabeled with 45CaCl2, basal Ca release into medium was at low level and was not modulated by treatment with avicatonin. The avicatonin, however, strongly suppressed the stimulated Ca release by bone resorption activators such as **1,25-dihydroxyvitamin D3**(1,25(OH)2D3), parathyroid hormone and prostaglandin E2. To elucidate the mechanism of the inhibitory effect of avicatonin on bone resorption, we examd. its effect on the generation of multinucleated cells, which indicate the characteristics as osteoclasts, in bone marrow cell culture. The multinucleated cells with 10 nuclei or more induced by 1,25(OH)2D3 showed high motility and contained tartrate-resistant acid phosphatase, a marker enzyme of osteoclasts. Simultaneous addn. of avicatonin with 1,25(OH)2D3 decreased the no. of multinucleated cells dose-dependency. Moreover, the avicatonin ceased the motility of the multinucleated cells and strikingly changed their shape within a few minutes after its addn. These results indicate that the potent **hypocalcemic** activity of avicatonin may be due to the inhibition of both of the generation and function of osteoclasts.

L20 ANSWER 16 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:691007 HCAPLUS
DOCUMENT NUMBER: 126:1661
TITLE: Long-term effects of intravenous **calcitriol** therapy on the control of secondary hyperparathyroidism
AUTHOR(S): Malberti, Fabio; Corradi, Bruno; Cosci, Paolo; Calliada, Fabrizio; Marcelli, Daniele; Imbasciati, Enrico
CORPORATE SOURCE: Department Dialysis and Radiology, Ospedale Maggiore, Lodi, Italy
SOURCE: Am. J. Kidney Dis. (1996), 28(5), 704-712
CODEN: AJKDDP; ISSN: 0272-6386
PUBLISHER: Saunders
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although high-dose i.v. **calcitriol** has been shown to be effective in suppressing parathyroid hormone (PTH) secretion in dialysis

patients with secondary hyperparathyroidism, an increasing no. of patients is refractory to treatment. Only a few studies have evaluated the factors that can predict a favorable response to **calcitriol**, but contrasting results have been reported. This study was performed to evaluate the effect of high-dose i.v. **calcitriol** on parathyroid function and to investigate the factors that can predict a favorable response to treatment. Thirty-five dialysis patients were selected for i.v. **calcitriol** treatment (2 .mu.g after dialysis for 12 mo) because of increased PTH levels (>325 pg/mL). Before starting the treatment, the set point of calcium and the PTH-ionized calcium (ICa) curve was evaluated in each patient by inducing **hypocalcemia** and, 1 wk later, hypercalcemia to maximally stimulate or inhibit PTH secretion. Parathyroid glands were assessed by high-resoln. color Doppler ultrasonog. Throughout the study, calcium carbonate or acetate dosage was modified to maintain serum phosphate less than 5.5 mg/dL. Hypercalcemia was managed by reducing dialyzate calcium to 5 mg/dL and, if necessary, **calcitriol** dose. The therapeutic goal was to reduce PTH levels below 260 pg/mL while maintaining normocalcemia. The patients who achieved the therapeutic goal were considered responders. Taking the data from the 35 patients together, we obsd. a significant decrease in alk. phosphatase (from 252 IU/L to 194 IU/L) and PTH (from 578 pg/mL to 408 pg/mL), and a significant increase in serum ICa (from 5.1 mg/dL to 5.3 mg/dL) after **calcitriol** therapy. PTH changes after therapy were not correlated to serum ICa changes, serum phosphate levels during treatment, and **calcitriol** dose. The response to therapy was heterogeneous because PTH levels markedly decreased over the treatment period in 18 responsive patients, whereas they increased or remained unchanged in 14 of 17 nonresponders. In three addnl. refractory patients, there was a decline in PTH of 20% to 35%, but this decline was assocd. with hypercalcemia. Pretreatment parathyroid gland size, serum ICa, PTH, maximal PTH induced by **hypocalcemia**, minimal PTH induced by hypercalcemia, the set point of ICa, and the ICa levels at which maximal PTH secretion and inhibition occurred were higher in the 17 refractory patients than in the 18 responsive patients. However, logistic regression anal. showed that among these parathyroid function parameters, the only significant predictors of a favorable response to **calcitriol** therapy were the parathyroid gland size and the set point of ICa. Throughout the study, serum phosphate and **calcitriol** dose were comparable in the two groups. In conclusion, the response to i.v. **calcitriol** therapy in dialysis patients with secondary hyperparathyroidism is heterogeneous, consisting of patients who are either responsive or refractory to treatment; refractoriness can be predicted by parathyroid vol. and calcium set point.

L20 ANSWER 17 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:296445 HCAPLUS
DOCUMENT NUMBER: 122:72621
TITLE: **Calcitriol** therapy and calcium-regulated PTH secretion in patients with secondary hyperparathyroidism
AUTHOR(S): Ramirez, Jorge A.; Goodman, William G.; Belin, Thomas R.; Gales, Barbara; Segre, Gino V.; Salusky, Isidro B.
CORPORATE SOURCE: Dep. Pediatrics, Univ. Calif. Los Angeles, Los Angeles, CA, 90024, USA
SOURCE: Am. J. Physiol. (1994), 267(6, Pt. 1), E961-E967
CODEN: AJPHAP; ISSN: 0002-9513
DOCUMENT TYPE: Journal
LANGUAGE: English
AB **Calcitriol** lowers serum parathyroid hormone (PTH) levels in patients with secondary hyperparathyroidism, but its effect on calcium-regulated PTH release remains controversial. Thus 11 patients with secondary hyperparathyroidism underwent dynamic tests of parathyroid function before and after 4 mo of intermittent **calcitriol** therapy. Serum **calcitriol** levels rose from 8 to 55 pg/mL, serum total and ionized calcium levels increased, and serum PTH levels decreased from 584 to 154 pg/mL,. The max. increase in serum PTH during **hypocalcemia** did not differ before (248 pg/mL) or after (280 pg/mL) treatment, but the increase in PTH, expressed as a percentage of preinfusion values, was greater after treatment (329 vs. 132%). The decreases in serum PTH during calcium infusions did not differ before (70%) or after (73%) therapy, and the set point for PTH release did not change (1.20 vs. 1.23 mmol/L, not significant). **Calcitriol** modifies PTH secretion during **hypocalcemia** in secondary

hyperparathyroidism without affecting the set point for PTH release; although **calcitriol** lowers serum PTH levels, it may also restore the secretory reserve of hyperplastic parathyroid tissues during **hypocalcemia**.

L20 ANSWER 18 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:535016 HCAPLUS
DOCUMENT NUMBER: 127:156540
TITLE: Serum parathyroid hormone and 25(OH)D3 before and after **calcitriol** treatment in childhood nephrotic syndrome
AUTHOR(S): Wang, Bingyan; Xu, Hao; Luo, Jingxiang; Chen, Jian; Ye, Tao; Li, Xiangjian; Le, Runhong
CORPORATE SOURCE: Dep. Nuclear Med. Affiliated Hospital, Med. College Ji'nan Univ., Canton, 510632, Peop. Rep. China
SOURCE: Guangdong Yixue (1997), 18(1), 3-4
CODEN: GUYIEG; ISSN: 1001-9448
PUBLISHER: Guangdongsheng Yixue Qingbao Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB Serum parathyroid hormone, 25(OH)D3 (**calcitriol**), calcium, phosphate and alk. phosphatase in 17 pediatric nephrotic syndrome before and after **calcitriol** pulsing therapy were studied and 18 healthy children served as control. After treatment with **calcitriol** the decreased calcium, 25(OH)D3 and the increased parathyroid hormone and alk. phosphatase were restored. The results suggest that the **hypocalcemia**, vitamin D metab. abnormalities and hyperparathyroidism in children suffering nephrotic syndrome received long-term high-dose glucocorticoid treatment is capable to be cor. by oral **calcitriol** pulsing therapy.

L20 ANSWER 19 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:557213 HCAPLUS
DOCUMENT NUMBER: 129:255507
TITLE: **Hypocalcemic** effect of osteoclastogenesis inhibitory factor/osteoprotegerin in the thyroparathyroidectomized rat
AUTHOR(S): Yamamoto, Michiko; Murakami, Takehiko; Nishikawa, Miyuki; Tsuda, Eisuke; Mochizuki, Shin-Ichi; Higashio, Kanji; Akatsu, Takuhiko; Motoyoshi, Kazuo; Nagata, Naokazu
CORPORATE SOURCE: Third Department of Internal Medicine, National Defense Medical College, Saitama, 359-8513, Japan
SOURCE: Endocrinology (1998), 139(9), 4012-4015
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Osteoclastogenesis inhibitory factor (OCIF), also termed as osteoprotegerin (OPG), is a sol. member of the tumor necrosis factor receptor family. Although OCIF/OPG is shown to inhibit osteoclast formation in vitro and prevent ovariectomy-induced bone loss in vivo, its effect on serum calcium level remains to be detd. In this study the authors examd. the acute effect of OCIF on thyroparathyroidectomized rats whose serum calcium concns. were raised either by exogenous PTH or 1,25-(OH)2D3. When OCIF was administered at the start of PTH infusion, it attenuated the initial rise in serum calcium. When OCIF was administered into rats with established hypercalcemia, it decreased serum calcium rapidly (within 2 h) and dramatically. OCIF did not increase urinary calcium excretion. These findings, esp. the rapid onset of its **hypocalcemic** effect, suggest that OCIF not only inhibits the formation of osteoclasts but also affects the function and/or survival of mature osteoclasts at doses used in this study.

L20 ANSWER 20 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:453196 HCAPLUS
DOCUMENT NUMBER: 125:133625
TITLE: Different effects of **calcitriol** and parathyroidectomy on the PTH-calcium curve in dialysis patients with severe hyperparathyroidism
AUTHOR(S): Malberti, F.; Corradi, B.; Cosci, P.; Colecchia, M.; Leopardi, O.; Grossi, L.; Oldini, C.; Imbasciati, E.
CORPORATE SOURCE: Servizio di Dialisi, Ospedale Maggiore, Lodi, 20075,

USA
SOURCE: Nephrol., Dial., Transplant. (1996), 11(1), 81-87
CODEN: NDTREA; ISSN: 0931-0509
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The PTH-calcium sigmoidal curve is shifted to the right, the slope of the curve is steeper, and the set point of calcium is increased in dialysis patients with secondary hyperparathyroidism, compared to patients with low-turnover bone disease. These findings could be related to increased parathyroid cells mass and increased sensitivity of parathyroid cells to serum calcium variations in these patients. **Calcitriol** therapy has been documented to reduce PTH levels by shifting the curve to the left and downward. The effect of a surgical redn. of parathyroid gland mass on the PTH-calcium curve has not yet been investigated. In this study we compared the effects of **calcitriol** and subtotal parathyroidectomy (PTH) on the dynamics of PTH secretion in response to acute changes of serum calcium in two groups of dialysis patients with severe hyperparathyroidism. Methods. Fourteen dialysis patients treated for 6 mo with high-dose i.v. **calcitriol** (1-2 .mu.g thrice weekly), and 10 dialysis patients who underwent subtotal PTx were studied. The PTH-calcium relationship obtained by inducing hypo- and hypercalcemia by means of low and high calcium dialysis was evaluated before and 2-6 mo after treatment. Results. Both **calcitriol** and subtotal PTx significantly decreased PTH (resp. from 797.+-.595 to 380.+-.244 and from 1036.+-.250 to 70.+-.34 pg/mL), as well as maximal PTH response to **hypocalcemia** (PTHmax), and maximal PTH suppression during hypercalcemia (PTHmin). When the PTH-calcium curves were constructed using PTHmax as 100% to factor for differences in abs. PTH levels and to provide an assessment of individual parathyroid cell function, a shift of the sigmoidal curve to the left and downward, and a significant decrease in the set point of ionized calcium (from 1.31.+-.0.05 to 1.26.+-.0.05 and from 1.36.+-.0.09 to 1.22.+-.0.07 mmol/l) was documented with both treatments. However, the slope of the PTH-calcium curve increased after subtotal PTx indicating that the sensitivity of the parathyroid cell to serum calcium changes increased with PTx, while on the contrary it decreased with **calcitriol**. Conclusions. PTH secretion decreases proportionally more with **calcitriol** than with surgery for a given decrease in the functional mass of parathyroid cells. The change in the PTH-ICa sigmoidal curve induced by subtotal PTx is due to the removal of a large mass of parathyroid tissue with advanced hyperplasia.

L20 ANSWER 21 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:183912 HCAPLUS
DOCUMENT NUMBER: 124:278716
TITLE: **Calcitriol** treatment of secondary hyperparathyroidism in chronic renal failure
AUTHOR(S): Malberti, F.
CORPORATE SOURCE: Servizio Dialisi, Ospedale Maggiore, Lodi, 20075, Italy
SOURCE: Ital. J. Miner. Electrolyte Metab. (1995), 9(2), 87-94
CODEN: IMEMEU; ISSN: 1121-1709
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pathogenetic factors contributing to the development of secondary hyperparathyroidism (HPT) in chronic renal failure (CRF) are multiple, with a major role played by phosphate retention, reduced availability of **calcitriol** and of its parathyroid gland receptors and skeletal resistance to the calcemic action of PTH. Phosphate restriction is crit. to the prevention and treatment of secondary HPT in mild to moderate CRF. Phosphate restriction may be obtained by dietary means or by use of phosphatase binders. **Calcitriol** therapy has been shown to decrease PTH levels and to improve bone mineralization. The potential risk of **calcitriol** therapy are hypercalcemia, hypercalciuria, hyperphosphatemia, and extraskeletal calcifications. **Calcitriol** therapy is recommended mostly in children, in patients with biochem. features of progressive bone disease and with longstanding renal failure. In many dialysis patients calcium supplements alone have been documented to be effective in controlling hyperphosphatemia, **hypocalcemia**, and progression of secondary HPT. However, there are patients who show a progressive increase in PTH levels, despite phosphatemia is adequately controlled and calcemia is maintained within the normal range by calcium supplements. In these patients long-term high-dose i.v. or oral **calcitriol** has proven to be more effective than the daily oral

administration in reducing PTH levels and reversing bone lesions.

L20 ANSWER 22 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:436258 HCAPLUS
DOCUMENT NUMBER: 133:84643
TITLE: Changes in bone turnover after parathyroidectomy in dialysis patients: role of **calcitriol** administration
AUTHOR(S): Mazzaferro, Sandro; Chicca, Silvana; Pasquali, Marzia; Zaraca, Francesco; Ballanti, Paola; Taggi, Franco; Coen, Giorgio; Cinotti, Giulio Alberto; Carboni, Manlio
CORPORATE SOURCE: Department of Clinical Science, University "La Sapienza", Rome, Italy
SOURCE: Nephrol., Dial., Transplant. (2000), 15(6), 877-882
CODEN: NDTREA; ISSN: 0931-0509
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Available data on changes in serum levels of bone markers after parathyroidectomy (PTx) in dialysis patients are not uniform. Changes are thought to be due to either a redn. in PTH activity per se or to a direct effect of vitamin D therapy on bone cells. We aimed to verify whether treatment with vitamin D modifies serum levels of markers of bone synthesis (alk. phosphatase (AP), osteocalcin (BGP), procollagen type I C-terminal peptide (PICP)) and resorption (collagen type I C-terminal peptide (ICTP)) within a period of 15 days in hemodialysis patients with severe secondary hyperparathyroidism following PTx. We randomized two groups (A, treatment and B, placebo, 10 patients each) with comparable basal PTH values and measured bone markers 3, 7 and 15 days after surgery. All patients were treated with calcium supplements (i.v. and p.o.), and group A also received **calcitriol** (2.4 .+-. 1.0 .mu.g/day, p.o.). In both groups, PTx induced significant changes in all the markers evaluated, except for BGP in group B. Compared to basal values, ICTP decreased from 481 .+-. 152 ng/mL in group A and 277 .+-. 126 ng/mL in group B to 267 .+-. 94 and 185 .+-. 71 ng/mL (M .+-. SD) resp., and PICP increased from 307 .+-. 139 ng/mL in group A and 309 .+-. 200 ng/mL in group B to 1129 .+-. 725 and 1231 .+-. 1267 ng/mL (M .+-. SD) resp., within 3 days of surgery. AP values increased after 15 days from 1115 .+-. 734 mU/mL in group A and 1419 .+-. 1225 mU/mL in group B to 1917 .+-. 1225 and 1867 .+-. 1295 mU/mL (M .+-. SD) resp. On the contrary, mean values of BGP were never different from basal levels after PTx in either group. In the two groups, the pattern of changes of all the bone markers after PTx was almost identical. Group A patients predictably required lower doses of oral calcium supplements to correct **hypocalcemia** (16.9 .+-. 5.7 vs 22.1 .+-. 5.0 g/10 days; M .+-. SD, $P < 0.04$). The opposite behavior of serum PICP and ICTP after PTx, in both the treated and untreated groups suggests that quant. uncoupling between bone synthesis and resorption is responsible for **hypocalcemia**. This phenomenon, as reflected by the evaluated bone markers, is unaffected by **calcitriol**. Based on our data we conclude that immediately after parathyroid surgery, vitamin D therapy does not influence bone cell activity, but improves **hypocalcemia** mainly through its known effect on intestinal calcium absorption.
REFERENCE COUNT: 21
REFERENCE(S): (9) Gram, J; Acta Endocrinol (Copenh) 1991, V125, P609 HCAPLUS
(11) Maierhofer, W; Kidney Int 1983, V24, P555 HCAPLUS
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(17) Stein, G; Endocr Rev 1993, V14, P424 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 23 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:535259 HCAPLUS
DOCUMENT NUMBER: 127:218941
TITLE: Effect of bicarbonate hemodialysis on plasma calcium in patients with chronic renal failure
AUTHOR(S): Cai, Xinlong
CORPORATE SOURCE: Dep. Med., Puning Hosp. Overseas, Puning, 515300, Peop. Rep. China
SOURCE: Guangdong Yixue (1997), 18(4), 247-248
CODEN: GUYIEG; ISSN: 1001-9448

PUBLISHER: Guangdongsheng Yixue Qingbao Yanjiuso
DOCUMENT TYPE: Journal
LANGUAGE: Chinese
AB The effect of bicarbonate hemodialysis on plasma calcium was studied in 137 patients with chronic renal failure. The plasma calcium before and after bicarbonate dialysis was 1.96 and 1.68 mmol/L, resp., P < 0.05, indicating a significant decrease after bicarbonate hemodialysis. Bicarbonate dialysis caused **hypocalcemia**-induced dryness of the skin and refractory itching, insomnia, muscle spasm and even convulsions. **Calcitriol** and calcium carbonate were helpful in prevention of the **hypocalcemia**. The results suggest that the dialysis formula warrant further improvement to avoid the occurrence of **hypocalcemia**.

L20 ANSWER 24 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:143207 HCAPLUS
DOCUMENT NUMBER: 126:234008
TITLE: Intravenous 1,25(OH)2D therapy increases the intact parathyroid hormone secretion set point in hemodialyzed patients
AUTHOR(S): Brossard, Jean-Hugues; Roy, Louise; Lepage, Raymond; Gascon-Barre, Marielle; D'amour, Pierre
CORPORATE SOURCE: Centre de Recherche Clinique Andre-Viallet, Hopital Saint-Luc, Montreal, PQ, H2X IP1, Can.
SOURCE: Miner. Electrolyte Metab. (1997), 23(1), 25-32
CODEN: MELMDI; ISSN: 0378-0392
PUBLISHER: Karger
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors studied the effect of i.v. **calcitriol** [1,25(OH)2D] therapy (1 .mu.g at the end of each dialysis session) on parathyroid secretory curves of hemodialyzed patients with near-normal basal intact (< 10 pM, NNBI) or elevated basal intact (> 10 pM, EBI) parathyroid hormone (PTH; iPTH) levels. These results were compared with those obtained in matched normal individuals (N). The main objective was to define the influence of i.v. 1,25(OH)2D therapy on the set point of iPTH stimulation in relation to the severity of secondary hyperparathyroidism. A complete parathyroid function was obtained by CaCl2 and Na2EDTA infusions in 14 N and by modification of the dialyzate calcium content in 13 hemodialyzed patients. Ionized calcium (Ca2+) and iPTH were measured regularly during hypo- and hypercalcemia. Parathyroid secretory curves were derived from these data. Both groups of patients had lower basal Ca2+ (NNBI 1.16; EBI 1.10; N 1.25 mM) and higher basal iPTH (NNBI 6.3; EBI 49.2; N 2.5 pM) levels than N with more extreme values in EBI than in NNBI patients. NNBI patients had stimulated iPTH levels similar to N (18.4 vs. 17.3 pM), while these levels were markedly increased in EBI patients (80.7 pM). After 1,25(OH)2D therapy, Ca2+ increased to 1.16 mM in EBI and normalized in NNBI patients (1.25 mM). Stimulated iPTH decreased by 30% in NNBI and by 21% in EBI patients. These two factors contributed to a decrease in basal iPTH by 52% in NNBI and by 40% in EBI. The set point of iPTH stimulation was lower than in N (1.8 mM) and increased with i.v. 1,25(OH)2D therapy from 1.09 to 1.16 mM in NNBI and from 1.08 to 1.12 mM in EBI patients. The set points and changes in set point were correlated with basal Ca2+ and changes in basal Ca2+ obsd. before and during therapy. The starting position of each patient on his secretory curve before and after 1,25(OH)2D therapy was inversely related to his starting Ca2+ concn. Taking this into account improved the relation between Ca2+ concn. and the set point of iPTH stimulation by Ca2+ in a stepwise regression. However, no correlation was found between set points and stimulated iPTH values. It is concluded that 1,25(OH)2D therapy induced an increase in the set point of PTH stimulation in **hypocalcemic** hemodialyzed patients related to a similar increase in basal Ca2+ concn. This is in part related to the starting position of each patient on his secretory curve which will affect his set point in relation to the hysteresis phenomenon in iPTH secretion. But the set point of PTH stimulation is also related to the basal ionized calcium concn. by mechanisms yet to be elucidated.

L20 ANSWER 25 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:734455 HCAPLUS
DOCUMENT NUMBER: 134:25180
TITLE: Role of vitamin D on the inhibition of gastrin production after cisplatin treatment
AUTHOR(S): Wang, Ying; Aggarwal, Surinder K.; Kopachik, Will

CORPORATE SOURCE: Department of Zoology, Michigan State University, East Lansing, MI, 48824-1115, USA
SOURCE: Met.-Based Drugs (2000), 7(3), 115-119
CODEN: MBADEI; ISSN: 0793-0291
PUBLISHER: Freund Publishing House Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In rats cisplatin induces **hypocalcemia**, bloating of the stomach, and ulceration ameliorated through calcium supplements. This study was undertaken to test the role of calcium on the gastrin mRNA prodn. in vitro and in vivo. RIN B6 cells were cultured in medium with calcium (1.8, 3.6 and 7.2 mM) and the active form of vitamin D (**calcijex**). Cisplatin was added (10 .mu.g/mL) for 12 h and cells were harvested for RNA from various treatment groups. Male Wistar rats were treated with cisplatin (9 mg/kg), before and after vitamin D (0.3 mg/100g/wk). The rats were killed and stomach tissues excised on 1, 6, 10 and 15 days after cisplatin treatment. RNA from the stomach was analyzed using the northern blot technique. Gastrin mRNA was suppressed after cisplatin treatment both in vitro and in vivo. In vitro calcium but not vitamin D addns. partially prevented the gastrin mRNA. In vivo, however, vitamin D and calcium were equally effective in preventing gastrin mRNA loss.

REFERENCE COUNT: 16
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L20 ANSWER 26 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:447075 HCAPLUS
DOCUMENT NUMBER: 125:123721
TITLE: Oral 1.alpha.-hydroxyprevitamin D
INVENTOR(S): Knutson, Joyce C.; Valliere, Charles R.; Bishop, Charles W.
PATENT ASSIGNEE(S): Lunar Corp., USA
SOURCE: U.S., 12 pp. Cont.-in-part of U.S. Ser. No. 901,886, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5529991	A	19960625	US 1994-196116	19940222
US 5622941	A	19970422	US 1994-188942	19940126
US 5614513	A	19970325	US 1995-485354	19950607
US 6147064	A	20001114	US 1995-476420	19950607
US 6150346	A	20001121	US 1995-474757	19950607
AU 9660608	A1	19961003	AU 1996-60608	19960722
AU 696402	B2	19980910		
US 6133250	A	20001017	US 1996-700798	19960821
US 5795882	A	19980818	US 1996-775447	19961230

PRIORITY APPLN. INFO.: US 1992-901886 B2 19920622
US 1994-188942 A3 19940126
US 1994-196116 A3 19940222
US 1995-485354 A2 19950607
OTHER SOURCE(S): MARPAT 125:123721

AB An enteric-coated sustained-release oral dosage form for vitamin D for treatment of osteoporosis and psoriasis and prevention of **hypocalcemia** and bone loss in hemodialysis is claimed. The compn. comprises a matrix contg. an activated vitamin D or 1.alpha.-hydroxy vitamin D coated with cellulose acetate phthalate or an acrylic polymer of Eudragit type.

L20 ANSWER 27 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:160112 HCAPLUS
DOCUMENT NUMBER: 128:255984

TITLE: Point mutations of the human parathyroid calcium receptor gene are not responsible for non-suppressible renal hyperparathyroidism
AUTHOR(S): Degenhardt, Stefan; Toell, Andrea; Weidemann, Wolfgang; Dotzenrath, Cornelia; Spindler, Klaus-Dieter; Grabensee, Bernd
CORPORATE SOURCE: Department of Nephrology and Rheumatology, Department of Hormone and Developmental Physiology, Heinrich Heine University, Dusseldorf, Germany
SOURCE: Kidney Int. (1998), 53(3), 556-561
CODEN: KDYIA5; ISSN: 0085-2538
PUBLISHER: Blackwell Science, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The calcium-dependent secretion of parathormone (PTH) is mediated through an extracellular G protein-coupled calcium receptor (CaR). Inactivating point mutations of this receptor have been found in familial **hypocalciuric** hypercalcemia and neonatal severe hyperparathyroidism. These diseases feature a decreased calcium sensitivity of the parathyroid glands, resulting in a rightward shift of the Ca2+-PTH relationship. Severe, non-suppressible renal hyperparathyroidism (rHPT) is often characterized by similar setpoint shifts to the right. Thus, point mutations of the CaR gene could contribute to non-suppressible rHPT. We examd. genomic DNA of hyperplastic or mainly nodular tissues of 39 parathyroids from 25 rHPT-patients with resistance to **calcitriol** therapy. Amplification of the six exons of the CaR gene was followed by single-strand conformation polymorphism (SSCP) anal. DNA sequencing was performed where band shifts were obsd. No point mutations in the coding sequence of the CaR gene were detected using the PCR-SSCP strategy. Point mutations in the coding regions of the CaR gene probably play no role in the evolution of renal HPT and are not responsible for the **calcitriol** resistance of PTH secretion.

L20 ANSWER 28 OF 28 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:426286 HCAPLUS
DOCUMENT NUMBER: 129:174337
TITLE: Osteopetrosis: pathogenesis and rationale for the use of interferon-.gamma.-1b
AUTHOR(S): Shankar, Lakshmi; Gerritsen, Egbert J. A.; Key, L. Lyndon, Jr
CORPORATE SOURCE: Department of Pediatrics and General Clinical Research Center, Medical University of South Carolina, Charleston, SC, USA
SOURCE: BioDrugs (1997), 7(1), 23-29
CODEN: BIDRF4; ISSN: 1173-8804
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 35 refs. Congenital osteopetrosis is a group of disorders resulting in decreased osteoclastic function and hence decreased bone resorption. Various medical treatments have been attempted to ameliorate the osteopetrotic condition. A calcium-deficient diet has limited further sclerosis in some patients. Prednisone therapy has improved haematol. function in some patients, but has not resulted in a redn. in bone mass. Calcitrophic hormones, such as parathyroid hormone (PTH) infusions and oral **calcitriol**, stimulate osteoclastic activity, and **calcitriol** in particular has stimulated osteoclastic bone resorption in some patients with osteopetrosis. Bone marrow transplantation, although curative, is limited by paucity of donors, risk of graft-vs.-host disease and relapse of the disease. The demonstration of defective leukocyte superoxide prodn. in osteopetrotic patients and the premise that osteoclasts appear to arise from the granulocyte macrophage lineage have led to attempts at treating osteopetrosis with immunomodulators. Since treatment with recombinant interferon-.gamma.-1b (interferon gamma-1b, IFN.gamma.-1b) has resulted in increased level of superoxide generation and clin. improvement in chronic granulomatous disease, a similar strategy has been employed using IFN.gamma.-1b to treat patients with osteopetrosis. IFN.gamma.-1b has been demonstrated to increase osteoclastic bone resorption and leukocytic function. Long term therapy with IFN.gamma.-1b by s.c. injection 3 times weekly resulted in marked clin. improvement, a decreased incidence of infections, a decreased trabecular bone mass, and an increased marrow space resulting in improved

hemopoiesis. The therapy has been assocd. with few adverse effects, mainly fever and diarrhea which have been managed with a redn. in IFN.gamma.-1b dosage. The low-calcium diet occasionally results in **hypocalcemic** tetany, which may be cor. by increased dietary calcium intake. Thus, IFN.gamma.-1b has a distinct place in the therapeutic armamentarium for patients with osteopetrosis and is a feasible treatment option in such patients.

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=> fil hcapl

=> s critical? ill or critical? care or icu
         84232 CRITICAL?
        291110 CRIT
            10 CRITS
        291116 CRIT
                  (CRIT OR CRITS)
        329330 CRITICAL?
                  (CRITICAL? OR CRIT)
          7154 ILL
            45 ILLS
          7193 ILL
                  (ILL OR ILLS)
           789 CRITICAL? ILL
                  (CRITICAL?(W)ILL)
         84232 CRITICAL?
        291110 CRIT
            10 CRITS
        291116 CRIT
                  (CRIT OR CRITS)
        329330 CRITICAL?
                  (CRITICAL? OR CRIT)
         23437 CARE
            95 CARES
         23520 CARE
                  (CARE OR CARES)
           186 CRITICAL? CARE
                  (CRITICAL?(W)CARE)
           426 ICU
            48 ICUS
           450 ICU
                  (ICU OR ICUS)
L21       1336 CRITICAL? ILL OR CRITICAL? CARE OR ICU

=> s parathyroid?
L22      15927 PARATHYROID?

=> s l21 and l22
L23         10 L21 AND L22

=> focus
PROCESSING COMPLETED FOR L23
L24          10 FOCUS L23 1-

=> d ibib abs kwic 1-5

L24  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:        1998:805351  HCAPLUS
DOCUMENT NUMBER:         130:208242
TITLE:                   Parathyroid hormone and ionized calcium
                         levels are related to the severity of illness and
                         survival in critically ill
                         patients
AUTHOR(S):               Carlstedt, F.; Lind, L.; Rastad, J.; Stjernstrom, H.;
                         Wide, L.; Ljunghall, S.
CORPORATE SOURCE:        University Hospital of Uppsala, Uppsala, S-751 85,
                         Swed.
SOURCE:                  Eur. J. Clin. Invest. (1998), 28(11), 898-903
                         CODEN: EJCIB8; ISSN: 0014-2972
PUBLISHER:               Blackwell Science Ltd.
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   The present study explores serum parathyroid hormone (PTH) and
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blood ionized calcium (Ca2+) levels in relation to the severity of disease and mortality in the intensive care unit (**ICU**). In a pilot study, 37 consecutive **critically ill** patients admitted to the **ICU** were studied with detns. of serum PTH and total serum calcium within the first 24 h. In a following prospective study, patients suffering from sepsis (n = 13) or subjected to major surgery (n = 13) were investigated daily for 1 wk with detns. of serum PTH and ionized calcium (Ca2+). Severity of disease was assessed by the APACHE II score and hospital mortality was recorded. In the pilot study, serum PTH levels were elevated (> 55 ng L-1) in 38% of the patients and were not related to serum calcium but showed a significant relationship to the APACHE II score (r = 0.39, P<0.05). In the prospective study, serum PTH was elevated in 69% of the patients in both groups at inclusion, and 6 days later 87% of the septic and 37% of the surgery patients still showed elevated levels. Hypocalcemia was more commonly seen in the septic patients [mean Ca2+ 1.03 .+-. 0.08 (SD) mmolL-1] than in the surgical patients (1.14 .+-. 0.06 mmolL-1) at inclusion. Both PTH and Ca2+ levels were significantly related to the APACHE II score (r = 0.46, P<0.03, and r = -0.54, P<0.009, resp.). Furthermore, PTH levels were significantly increased in non-survivors (n = 5) compared with survivors (mean 161 .+-. 51 vs. 79 .+-. 51 ngL-1, P<0.005). Hypocalcemia and increased levels of PTH were common findings in **critically ill** patients. These alterations in calcium homeostasis were related to the severity of disease and increased PTH levels were assocd. with a poor outcome.

REFERENCE COUNT: 37

REFERENCE(S):
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(10) Dinarello, C; Curr Top Microbiol Immunol 1996, V216, P133 HCAPLUS
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Parathyroid** hormone and ionized calcium levels are related to the severity of illness and survival in **critically ill** patients

AB The present study explores serum **parathyroid** hormone (PTH) and blood ionized calcium (Ca2+) levels in relation to the severity of disease and mortality in the intensive care unit (**ICU**). In a pilot study, 37 consecutive **critically ill** patients admitted to the **ICU** were studied with detns. of serum PTH and total serum calcium within the first 24 h. In a following prospective study, patients suffering from sepsis (n = 13) or subjected to major surgery (n = 13) were investigated daily for 1 wk with detns. of serum PTH and ionized calcium (Ca2+). Severity of disease was assessed by the APACHE II score and hospital mortality was recorded. In the pilot study, serum PTH levels were elevated (> 55 ng L-1) in 38% of the patients and were not related to serum calcium but showed a significant relationship to the APACHE II score (r = 0.39, P<0.05). In the prospective study, serum PTH was elevated in 69% of the patients in both groups at inclusion, and 6 days later 87% of the septic and 37% of the surgery patients still showed elevated levels. Hypocalcemia was more commonly seen in the septic patients [mean Ca2+ 1.03 .+-. 0.08 (SD) mmolL-1] than in the surgical patients (1.14 .+-. 0.06 mmolL-1) at inclusion. Both PTH and Ca2+ levels were significantly related to the APACHE II score (r = 0.46, P<0.03, and r = -0.54, P<0.009, resp.). Furthermore, PTH levels were significantly increased in non-survivors (n = 5) compared with survivors (mean 161 .+-. 51 vs. 79 .+-. 51 ngL-1, P<0.005). Hypocalcemia and increased levels of PTH were common findings in **critically ill** patients. These alterations in calcium homeostasis were related to the severity of disease and increased PTH levels were assocd. with a poor outcome.

ST **parathyroid** hormone ionized calcium sepsis crit illness outcome

IT Diseases (animal)
(crit. illness; **parathyroid** hormone in human serum and blood Ca2+ levels in relation to severity of disease and mortality in intensive care unit)

IT Surgery
(major; **parathyroid** hormone in human serum and blood Ca2+ levels in relation to severity of disease and mortality in intensive care unit)

IT Biomarkers (biological responses)
Blood analysis
Death (animal)

Hypocalcemia
Prognosis
Sepsis
(**parathyroid** hormone in human serum and blood Ca2+ levels in relation to severity of disease and mortality in intensive care unit)

IT 9002-64-6, **Parathyroid** hormone 14127-61-8, Ca2+, biological studies
RL: BOC (Biological occurrence); THU (Therapeutic use); BIOL (Biological study); OCCU (Occurrence); USES (Uses)
(**parathyroid** hormone in human serum and blood Ca2+ levels in relation to severity of disease and mortality in intensive care unit)

L24 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:5430 HCAPLUS
DOCUMENT NUMBER: 112:5430
TITLE: Calcium homeostasis in the **critically ill** patient
AUTHOR(S): Zaloga, Gary P.
CORPORATE SOURCE: Bowman Gray Sch. Med., Wake Forest Univ., Winston-Salem, NC, USA
SOURCE: Magnesium (1989), 8(3-4), 190-200
CODEN: MAGND2; ISSN: 0252-1156
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review with 23 refs. The serum concn. of ionized calcium is the physiol. active circulating calcium fraction, and its level is influenced by protein binding, pH and free fatty acid levels. Hypocalcemia is common in **crit. ill** patients and primarily results from abnormalities in the **parathyroid**-vitamin D axis and circulating chelators. Hypercalcemia is less common and primarily results from malignancy, hyperparathyroidism, and posthypocalcemic hypercalcemia. Mild hypocalcemia and hypercalcemia are well tolerated. Severe hypocalcemia may cause cardiovascular compromise and impair drug action. In ischemic and shock states, hypercalcemia may be detrimental and calcium channel blockers may be useful.
TI Calcium homeostasis in the **critically ill** patient
AB A review with 23 refs. The serum concn. of ionized calcium is the physiol. active circulating calcium fraction, and its level is influenced by protein binding, pH and free fatty acid levels. Hypocalcemia is common in **crit. ill** patients and primarily results from abnormalities in the **parathyroid**-vitamin D axis and circulating chelators. Hypercalcemia is less common and primarily results from malignancy, hyperparathyroidism, and posthypocalcemic hypercalcemia. Mild hypocalcemia and hypercalcemia are well tolerated. Severe hypocalcemia may cause cardiovascular compromise and impair drug action. In ischemic and shock states, hypercalcemia may be detrimental and calcium channel blockers may be useful.
IT Blood
(calcium of, in **crit. ill** humans, therapy in relation to)
IT 7440-70-2, Calcium, biological studies
RL: BIOL (Biological study)
(metabolic disorders, hypocalcemia and hypercalcemia, in **crit. ill** humans, therapy in relation to)

L24 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:350241 HCAPLUS
DOCUMENT NUMBER: 131:86737
TITLE: Interleukin-6 induced suppression of bovine **parathyroid** hormone secretion
AUTHOR(S): Carlstedt, E.; Ridefelt, P.; Lind, L.; Rastad, J.
CORPORATE SOURCE: Department of Medicine, University Hospital of Uppsala, Uppsala, 75185, Swed.
SOURCE: Biosci. Rep. (1999), 19(1), 35-42
CODEN: BRPTDT; ISSN: 0144-8463
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effects of tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-6 (IL-6) on **parathyroid** hormone (PTH) secretion were investigated. IL-6 and TNF-.alpha. had no acute effect on PTH secretion in extracellular Ca2+ concns. of 0.5, 1.25 and 3.0 mM. In contrast to TNF-.alpha., cultures for 24 h in the presence of 10 ng/mL of IL-6 showed

decreased PTH secretion by 51% and 29% in 0.5 mM and 1.25 mM Ca2+ resp. Neither IL-6 nor TNF-.alpha. affected cytoplasmic Ca2+ of the cells. Thus, PTH secretion in vitro can be suppressed by IL-6 at clin. relevant concns. This suppression may aggravate hypocalcemia of the **critically ill** and attenuate the conventionally strong stimulation of the PTH release by redn. in serum calcium.

REFERENCE COUNT: 27

REFERENCE(S):
(3) Brown, E; Phys Rev 1991, V71, P371 HCAPLUS
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(16) Hotchkiss, R; New Horiz 1996, V4, P58 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Interleukin-6 induced suppression of bovine **parathyroid** hormone secretion

AB The effects of tumor necrosis factor-.alpha. (TNF-.alpha.) and interleukin-6 (IL-6) on **parathyroid** hormone (PTH) secretion were investigated. IL-6 and TNF-.alpha. had no acute effect on PTH secretion in extracellular Ca2+ concns. of 0.5, 1.25 and 3.0 mM. In contrast to TNF-.alpha., cultures for 24 h in the presence of 10 ng/mL of IL-6 showed decreased PTH secretion by 51% and 29% in 0.5 mM and 1.25 mM Ca2+ resp. Neither IL-6 nor TNF-.alpha. affected cytoplasmic Ca2+ of the cells. Thus, PTH secretion in vitro can be suppressed by IL-6 at clin. relevant concns. This suppression may aggravate hypocalcemia of the **critically ill** and attenuate the conventionally strong stimulation of the PTH release by redn. in serum calcium.

ST interleukin 6 **parathyroid** hormone calcium hypocalcemia

IT Interleukin 6
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(interleukin-6 induced suppression of **parathyroid** hormone secretion in hypocalcemia)

IT Tumor necrosis factors
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(interleukin-6 induced suppression of **parathyroid** hormone secretion in hypocalcemia)

IT 7440-70-2, Calcium, biological studies
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(hypocalcemia; interleukin-6 induced suppression of **parathyroid** hormone secretion in hypocalcemia)

IT 7440-70-2, Calcium, biological studies
RL: BOC (Biological occurrence); BIOL (Biological study); OCCU (Occurrence)
(interleukin-6 induced suppression of **parathyroid** hormone secretion in hypocalcemia)

IT 9002-64-6, **Parathyroid** hormone
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(interleukin-6 induced suppression of **parathyroid** hormone secretion in hypocalcemia)

L24 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:717727 HCAPLUS

DOCUMENT NUMBER: 134:261188

TITLE: Biochemical response to treatment of bone hyperresorption in chronically critically III patients

AUTHOR(S): Nierman, David M.; Mechanick, Jeffrey I.

CORPORATE SOURCE: Department of Medicine, Mount Sinai Medical Center, New York, NY, 10029-6574, USA

SOURCE: Chest (2000), 118(3), 761-766
CODEN: CHETBF; ISSN: 0012-3692

PUBLISHER: American College of Chest Physicians

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Study objective: The chronically **critically ill** (CCI) are a subgroup of **critically ill** patients who have survived an acute crit. illness but remain profoundly debilitated and ventilator dependent. We have previously shown that CCI patients have a very high prevalence of bone hyperresorption. The objective of this present study was to det. the biochem. response of bone hyperresorption in CCI patients to treatment with either calcitriol alone or calcitriol and

pamidronate. Design: Retrospective survey. Setting: Respiratory care step-down unit (RCU) at a tertiary-care teaching hospital. Patients: Fifty-five ventilator-dependent CCI patients transferred from **ICUs** within the same institution who had elevated urine N-telopeptide (NTx) levels at RCU admission, who were treated with either calcitriol alone (n = 44) or calcitriol and pamidronate (n = 11), and who had urine NTx levels remeasured following treatment. Intervention: None. Measurements and results: Patients treated with calcitriol alone had a significant redn. in serum **parathyroid** hormone (PTH; 93.+-.145 pg/mL vs. 40.+-.28 pg/mL; p = 0.02) but not in urinary NTx (187.+-.146 nmol bone collagen equiv. [BCE]/mmol creatinine [Cr] vs 178.+-.123 nmol BCE/mmol Cr, p = 0.59). In contrast, patients treated with both calcitriol and pamidronate had a significant decrease in urine NTx at follow-up (329.+-.238 to 100.+-.85 nmol BCE/mmol Cr; p < 0.01) but not in serum PTH (36.+-.29 to 53.+-.51 pg/mL; p = 0.44). Conclusion: The bone hyperresorption of CCI patients is PTH independent and biochem. responds to treatment with calcitriol and pamidronate but not calcitriol alone.

REFERENCE COUNT: 21

REFERENCE(S):
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(14) Rosen, H; Calcif Tissue Int 1994, V54, P26 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Study objective: The chronically **critically ill** (CCI) are a subgroup of **critically ill** patients who have survived an acute crit. illness but remain profoundly debilitated and ventilator dependent. We have previously shown that CCI patients have a very high prevalence of bone hyperresorption. The objective of this present study was to det. the biochem. response of bone hyperresorption in CCI patients to treatment with either calcitriol alone or calcitriol and pamidronate. Design: Retrospective survey. Setting: Respiratory care step-down unit (RCU) at a tertiary-care teaching hospital. Patients: Fifty-five ventilator-dependent CCI patients transferred from **ICUs** within the same institution who had elevated urine N-telopeptide (NTx) levels at RCU admission, who were treated with either calcitriol alone (n = 44) or calcitriol and pamidronate (n = 11), and who had urine NTx levels remeasured following treatment. Intervention: None. Measurements and results: Patients treated with calcitriol alone had a significant redn. in serum **parathyroid** hormone (PTH; 93.+-.145 pg/mL vs. 40.+-.28 pg/mL; p = 0.02) but not in urinary NTx (187.+-.146 nmol bone collagen equiv. [BCE]/mmol creatinine [Cr] vs 178.+-.123 nmol BCE/mmol Cr, p = 0.59). In contrast, patients treated with both calcitriol and pamidronate had a significant decrease in urine NTx at follow-up (329.+-.238 to 100.+-.85 nmol BCE/mmol Cr; p < 0.01) but not in serum PTH (36.+-.29 to 53.+-.51 pg/mL; p = 0.44). Conclusion: The bone hyperresorption of CCI patients is PTH independent and biochem. responds to treatment with calcitriol and pamidronate but not calcitriol alone.

L24 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2001:284676 HCAPLUS

DOCUMENT NUMBER: 135:44421

TITLE: **Parathyroid** hormone-related protein-(1-36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy

AUTHOR(S): Syed, Mushtaq A.; Horwitz, Mara J.; Tedesco, Mary Beth; Garcia-Ocana, Adolfo; Wisniewski, Stephen R.; Stewart, Andrew F.

CORPORATE SOURCE: Division of Endocrinology and Metabolism, University of Pittsburgh School of Medicine, Pittsburgh, PA, 15213, USA

SOURCE: J. Clin. Endocrinol. Metab. (2001), 86(4), 1525-1531
CODEN: JCEMAZ; ISSN: 0021-972X

PUBLISHER: Endocrine Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB All would agree that hypercalcemia occurs among patients with humoral hypercalcemia of malignancy (HHM) as a result of osteoclastic bone

resorption. Some studies suggest that enhanced renal calcium resorption, which plays an important pathophysiol. role in the hypercalcemia occurring in primary hyperparathyroidism, is also important pathophysiol. in HHM. Other studies have not agreed. In large part, these differences result from the inability to accurately assess creatinine and calcium clearance in **critically ill** subjects with HHM. To circumvent these issues, we have developed steady state 48-h PTH-related protein (PTHrP) infusion and 8-h hypercalcemic calcium clamp protocols. These techniques allow assessment of the effects of steady state PTHrP and calcium infusions in normal healthy volunteers in a setting in which renal function is stable and measurable and in which the filtered load of calcium can be matched in PTHrP- and calcium-infused subjects. Normal subjects were infused with saline (placebo), PTHrP, or calcium. Subjects receiving PTHrP, as expected, displayed mild hypercalcemia (10.2 mg/dL), suppression of endogenous PTH-(1-84), and phosphaturia. Subjects receiving the hypercalcemic calcium clamp displayed indistinguishable degrees of hypercalcemia and PTH suppression. Despite their matched degrees of hypercalcemia and PTH suppression, the two groups differed importantly with regard to fractional calcium excretion (FECa). The hypercalcemic calcium clamp group was markedly hypercalciuric (FECa averaged 6.5%), whereas FECa in the PTHrP-infused subjects was approx. 50% lower (between 2.5-3.7%), and no different from that in the normal controls, which ranged from 1.5-3.0%. These studies demonstrate that PTHrP is able to stimulate renal calcium resorption in healthy volunteers. These studies suggest that PTHrP-induced renal calcium resorption, in concert with the well established acceleration of osteoclastic bone resorption, contributes in a significant way to the hypercalcemia obsd. in patients with HHM.

REFERENCE COUNT: 39
REFERENCE(S):
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(5) Burtis, W; J Clin Endocrinol Metab 1994, V78, P317 HCAPLUS
(8) Everhart-Caye, M; J Clin Endocrinol Metab 1996, V81, P199 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI **Parathyroid** hormone-related protein-(1-36) stimulates renal tubular calcium reabsorption in normal human volunteers: implications for the pathogenesis of humoral hypercalcemia of malignancy

AB All would agree that hypercalcemia occurs among patients with humoral hypercalcemia of malignancy (HHM) as a result of osteoclastic bone resorption. Some studies suggest that enhanced renal calcium resorption, which plays an important pathophysiol. role in the hypercalcemia occurring in primary hyperparathyroidism, is also important pathophysiol. in HHM. Other studies have not agreed. In large part, these differences result from the inability to accurately assess creatinine and calcium clearance in **critically ill** subjects with HHM. To circumvent these issues, we have developed steady state 48-h PTH-related protein (PTHrP) infusion and 8-h hypercalcemic calcium clamp protocols. These techniques allow assessment of the effects of steady state PTHrP and calcium infusions in normal healthy volunteers in a setting in which renal function is stable and measurable and in which the filtered load of calcium can be matched in PTHrP- and calcium-infused subjects. Normal subjects were infused with saline (placebo), PTHrP, or calcium. Subjects receiving PTHrP, as expected, displayed mild hypercalcemia (10.2 mg/dL), suppression of endogenous PTH-(1-84), and phosphaturia. Subjects receiving the hypercalcemic calcium clamp displayed indistinguishable degrees of hypercalcemia and PTH suppression. Despite their matched degrees of hypercalcemia and PTH suppression, the two groups differed importantly with regard to fractional calcium excretion (FECa). The hypercalcemic calcium clamp group was markedly hypercalciuric (FECa averaged 6.5%), whereas FECa in the PTHrP-infused subjects was approx. 50% lower (between 2.5-3.7%), and no different from that in the normal controls, which ranged from 1.5-3.0%. These studies demonstrate that PTHrP is able to stimulate renal calcium resorption in healthy volunteers. These studies suggest that PTHrP-induced renal calcium resorption, in concert with the well established acceleration of osteoclastic bone resorption, contributes in a significant way to the hypercalcemia obsd. in patients with HHM.

IT 172867-62-8, 1-36-Human **parathyroid** hormone-related protein
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)

(PTHrP (1-36) stimulates renal tubular calcium reabsorption in normal human volunteers in relation to pathogenesis of humoral hypercalcemia of malignancy)

IT 9002-64-6, **Parathyroid** hormone 68893-82-3, Human **parathyroid** hormone 1-84
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(in plasma; PTHrP (1-36) stimulates renal tubular calcium reabsorption in normal human volunteers in relation to pathogenesis of humoral hypercalcemia of malignancy)

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L24 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1977:500917 HCAPLUS
DOCUMENT NUMBER: 87:100917
TITLE: Metabolic response of laying hens to different dietary levels of calcium, phosphorus and vitamin D3
AUTHOR(S): Antillon, Armando; Scott, Milton L.; Krook, Lennart; Wasserman, Robert H.
CORPORATE SOURCE: New York State Coll. Vet. Med., Cornell Univ., Ithaca, N. Y., USA
SOURCE: Cornell Vet. (1977), 67(3), 413-44
CODEN: COVEAZ
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The performance of laying hens fed the recommended levels of Ca (3.6%), P (0.55%) and vitamin D3 [67-97-0] (1180 **ICU**/kg) was compared to that of hens fed lower levels of Ca (2 and 1%) or lower levels of P (0.26 and 0.13%) or lower levels vitamin D3 (300 and 80 **ICU**/kg and 660 and 0 **ICU**/kg, the latter levels with a purified diet). The recommended levels of Ca and vitamin D supported high egg prodn., fairly good egg shell strength, normal levels of Ca-binding protein (CaBP) in intestine and uterus, and normal **parathyroid** activity and bone metab. A decrease from 0.55 to 0.26% in dietary P resulted in decreased feed consumption, increased egg prodn. and increased egg shell strength. The main osseous source of egg shell Ca is the medullary bone as evidenced by the great normal turnover rate in that bone. With Ca or vitamin D deficiency, medullary bone was resorbed in excess; cortical bone loss was less severe. With 80 **ICU** Vitamin D3/kg of diet, CaBP formation, egg prodn. and egg shell strength decreased, and **parathyroid** activity and bone resorprtion increased during the 1st 50 days of the expt. During the subsequent 50 days, **parathyroid** activity returned to normal and medullary bone was restored. CaBP began to rise, egg prodn. resumed and shell strength improved at this time. Following this apparent recovery, hyperparathyroidism with excessive bone resorption occurred once again. The 2nd observation period was too short for a possible repetition of the events which had occurred during the 1st 100 days. Ca metab. in these hens receiving a sub-marginal level of vitamin D3 appeared to show a cycling normal activity, followed by a cycle of severe vitamin D3-deficiency metab.

IT **Parathyroid** gland
(in egg production, calcium, phosphorus and vitamin D3 effect on)

IT Chicken
(**parathyroid** and bone metab. by, calcium, phosphorus, and vitamin D3 effect on)

L24 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:708596 HCAPLUS
DOCUMENT NUMBER: 134:161098
TITLE: Disordered calcium homeostasis of sepsis. Association with calcitonin precursors
AUTHOR(S): Muller, B.; Becker, K. L.; Kranzlin, M.; Schachinger, H.; Huber, P. R.; Nylen, E. S.; Snider, R. H.; White, J. C.; Schmidt-Gayk, H.; Zimmerli, W.; Ritz, R.
CORPORATE SOURCE: Division of Medical Intensive Care, University Hospitals, Basel, CH-4031, Switz.
SOURCE: Eur. J. Clin. Invest. (2000), 30(9), 823-831
CODEN: EJCIB8; ISSN: 0014-2972
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Hypocalcemia and increased blood serum levels of calcitonin precursors are common in **critically ill** patients, esp. in those with sepsis. The authors investigated Ca homeostasis in such patients. Serum concns. of total and ionized Ca and known factors influencing or reflecting Ca homeostasis were measured in 101 consecutive patients of a medical intensive care unit. Calcitonin precursor levels were detd. using a highly sensitive RIA. Crit. illness per se was assocd. with decreased serum total and ionized Ca levels, which correlated with the severity of the underlying disease as measured by the APACHE II score. In addn., total and ionized hypocalcemia was more pronounced with increasing severity of infection (P <0.02), and occurred in parallel with a marked increase of calcitonin precursors (P <0.001). Mature calcitonin levels, however, remained normal. Changes of serum ionized Ca concns. from admission to discharge correlated significantly with changes in the serum calcitonin precursor concn. (r2 = -0..cntdot.14, P <0.001). Circulating vitamin D levels, **parathyroid** hormone levels and other markers reflecting Ca homeostasis did not correlate with the severity of infection. In **critically ill** patients with sepsis, markedly elevated circulating calcitonin precursors might play a role in the development of the pronounced hypocalcemia. The specific calcitonin precursor(s) responsible for this effect and the pathophysiol. mechanism remain to be elucidated.

REFERENCE COUNT: 56

REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

AB Hypocalcemia and increased blood serum levels of calcitonin precursors are common in **critically ill** patients, esp. in those with sepsis. The authors investigated Ca homeostasis in such patients. Serum concns. of total and ionized Ca and known factors influencing or reflecting Ca homeostasis were measured in 101 consecutive patients of a medical intensive care unit. Calcitonin precursor levels were detd. using a highly sensitive RIA. Crit. illness per se was assocd. with decreased serum total and ionized Ca levels, which correlated with the severity of the underlying disease as measured by the APACHE II score. In addn., total and ionized hypocalcemia was more pronounced with increasing severity of infection (P <0.02), and occurred in parallel with a marked increase of calcitonin precursors (P <0.001). Mature calcitonin levels, however, remained normal. Changes of serum ionized Ca concns. from admission to discharge correlated significantly with changes in the serum calcitonin precursor concn. (r2 = -0..cntdot.14, P <0.001). Circulating vitamin D levels, **parathyroid** hormone levels and other markers reflecting Ca homeostasis did not correlate with the severity of infection. In **critically ill** patients with sepsis, markedly elevated circulating calcitonin precursors might play a role in the development of the pronounced hypocalcemia. The specific calcitonin precursor(s) responsible for this effect and the pathophysiol. mechanism remain to be elucidated.

L24 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:788489 HCAPLUS
DOCUMENT NUMBER: 130:177436
TITLE: Plasma electrolyte and metabolite concentrations associated with pentobarbital or pentobarbital-propofol anesthesia during three weeks' mechanical ventilation and intensive care in dogs
AUTHOR(S): Gronert, Gerald A.; Haskins, Steve C.; Steffey, Eugene P.; Fung, Dennis
CORPORATE SOURCE: Department of Anesthesiology, School of Medicine, University of California, Davis, CA, USA
SOURCE: Lab. Anim. Sci. (1998), 48(5), 513-519
CODEN: LBASAE; ISSN: 0023-6764
PUBLISHER: American Association for Laboratory Animal Science
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Propofol and pentobarbital were used for deep sedation during prolonged

mech. ventilation (3 wk) and nutritional supplementation in 17 clin. normal dogs in an intensive care setting. Tolerance developed to both drugs. Propofol, in combination with pentobarbital, at an infusion rate of 75 .mu.g/kg of body wt. per min was preferred. Pentobarbital infusion alone, begun at the rate of 5 to 6 mg.bul.kg-1.bul.h-1, was satisfactory. The combination of both drugs provided smooth, stable anesthesia and required minimal interventions by intensive care unit personnel. Blood gas tensions and electrolyte, **parathyroid** hormone (PTH), and metabolite concns. were generally stable throughout, unless condition of the dog deteriorated (e.g., infection, pneumothorax). Hematocrit and red blood cell count decreased with time, likely attributable principally to multiple blood sample collections. White blood cell count, alk. phosphatase, phosphate, fibrinogen, cholesterol, and triglyceride values increased with time, in assocn. with pentobarbital and the combination of pentobarbital and propofol. Some of these changes appear to have been related to generic responses to stress and inflammation, some to altered metab., and some to the lipid solvent of propofol. The increase in triglyceride concn. was greater when propofol was used. Mortality was 47%, with death occurring between days 2 and 18.

REFERENCE COUNT: 7
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:586507 HCAPLUS
DOCUMENT NUMBER: 132:121857

TITLE: Acute effects of calcium sodium citrate supplementation of a test meal on mineral homeostasis, oxalate, and calcium oxalate crystallization in the urine of healthy humans - preliminary results in patients with idiopathic calcium urolithiasis

AUTHOR(S): Herrmann, U.; Schwille, P. O.; Schmiedl, A.; Fan, J.; Manoharan, M.
CORPORATE SOURCE: Mineral Metabolism and Endocrine Research Laboratory, Departments of Surgery and Urology, University of Erlangen, Erlangen, 91023, Germany

SOURCE: Biomed. Pharmacother. (1999), 53(5/6), 264-273
CODEN: BIPHEX; ISSN: 0753-3322
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Ca food supplementation can improve bone metab., but it can also increase the risk for renal Ca stones and may aggravate pre-existing Ca urolithiasis. The renal Ca stone formation risk was studied in 10 healthy humans (5 men, 5 women) given a conventional test breakfast (28 mg Ca) with or without 2 dosages of calcium-sodium citrate (CSC-1, 680 mg Ca; CSC-2 1360 mg Ca), taken after an overnight 12-h fast. The aggravation of pre-existing Ca urolithiasis was studied in 14 patients with idiopathic recurrent calcium urolithiasis (**ICU**) given a balanced test meal of fixed compn. contg. 1000 mg Ca as CSC (M+CSC3) or as Ca gluconate (M). In the normal subjects, CSC induced a dose-dependent increase in intestinal Ca absorption and a decrease in oxalate absorption; in blood serum CSC increased calcitonin and suppressed **parathyroid** hormone levels, but left unchanged the markers of bone turnover (serum osteocalcin and bone alk. phosphatase). In urine, CSC decreased bone resorption markers (collagen crosslinks) and phosphaturia, increased citrate concns., created signs of metabolic alkalosis, and inhibited several parameters of Ca oxalate crystn. In **ICU** patients the CSC3 load failed to promote the crystn. of Ca oxalate and Ca phosphate. Thus, dietary CSC supplementation is well tolerated by healthy subjects and **ICU** patients and renders Ca highly available to bones. It prevents postprandial oxaluria increase and is followed by the inhibition of crystn. of renal stone-forming Ca-contg. substances.

REFERENCE COUNT: 46
REFERENCE(S):
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ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:182205 HCAPLUS
DOCUMENT NUMBER: 135:44606
TITLE: Screening for primary hyperparathyroidism (PHPT) in clinic patients: differential diagnosis between PHPT and malignancy-associated hypercalcemia by routine blood tests
AUTHOR(S): Kim, S. J.; Shiba, E.; Maeda, I.; Yoshioka, T.; Amino, N.; Noguchi, S.
CORPORATE SOURCE: Departments of Surgical Oncology, 2-2-E-10 Yamadaoka, Osaka University Medical School, Osaka, Suita City, 565-0871, Japan
SOURCE: Clin. Chim. Acta (2001), 305(1-2), 35-40
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Screening for primary hyperparathyroidism (PHPT) by measurement of the serum calcium concn. detects one patient per 500-1000 individuals in Western countries, and one patient per 2500-5000 subjects in Japan. Among clinic patients, however, the presence of many false-pos. cases due to malignancy-assocd. hypercalcemia (MAH) reduces the benefit of such screening. We evaluated a new method of screening for PHPT based on the results of routine blood tests using the hospital information system (HIS) at our hospital. This new method could distinguish PHPT from MAH. This study included 25179 blood samples in which the serum calcium (Ca), albumin (Alb), chloride (Cl) and inorg. phosphate (IP) concns. The HIS was programmed to pick blood samples that satisfied Formula 1 [Ca(mEq/mL)>0.3.times.Alb(g/dL)+4.1] and Formula 2 {[Cl(mEq/mL)-84].times.[10.times.Alb-15].div.[IP(mg/dL).div.3.1]>400). Of data from 25179 blood samples collected, those from 54 patients satisfied both Formulas 1 and 2. The patients from which these samples were derived from were subject to further anal.: medical records were studied and the intact-**parathyroid** hormone concn. was measured if necessary. Of these 54 cases, 19 patients (35.2%) were subsequently diagnosed with PHPT, including two, who were newly diagnosed with PHPT by this screening procedure. Although 35 (64.8%) of 54 patients were false-pos., many of them were treated with blood purifn. therapies. On the other hand, there were four false-pos. cases (7.4%) caused by MAH. False-neg. case in this study was only one patient (5%), whose diagnosis was normocalcemic PHPT. When omitting samples from pediatric patients and those in **ICU**, this screening procedure for PHPT has the advantage of being able to differentiate this diagnosis from MAH.

REFERENCE COUNT: 25
REFERENCE(S): (5) Ellis, A; J Endocrinol 1990, V126, P403 HCAPLUS
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IT 9002-64-6, **Parathyroid** hormone
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AB A review with 23 refs. The serum concn. of ionized calcium is the physiol. active circulating calcium fraction, and its level is influenced by protein binding, pH and free fatty acid levels. Hypocalcemia is common in **crit. ill** patients and primarily results from abnormalities in the **parathyroid**-vitamin D axis and circulating chelators. Hypercalcemia is less common and primarily results from malignancy, hyperparathyroidism, and posthypocalcemic hypercalcemia. Mild hypocalcemia and hypercalcemia are well tolerated. Severe hypocalcemia may cause cardiovascular compromise and impair drug action. In ischemic and shock states, hypercalcemia may be detrimental and calcium channel blockers may be useful.

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Calcium Homeostasis in the Critically Ill Patient

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Key Words. Calcium · Hypocalcemia · Hypercalcemia · Critical care

Abstract. The serum concentration of ionized calcium is the physiologically active circulating calcium fraction, and its level is influenced by protein binding, pH and free fatty acid levels. Hypocalcemia is common in critically ill patients and primarily results from abnormalities in the parathyroid-vitamin-D axis and circulating chelators. Hypercalcemia is less common and primarily results from malignancy, hyperparathyroidism and posthypocalcemic hypercalcemia. Mild degrees of hypocalcemia and hypercalcemia are well tolerated. However, severe hypocalcemia may cause cardiovascular compromise and impair drug action. In ischemic and shock states, hypercalcemia may be detrimental, and calcium channel blockers may be useful.

Calcium (Ca) is essential for normal cellular function. Ca movement into the cell and release from intracellular sites is vital for the coupling of receptor-stimulated cellular events to cellular responses. Ca is required for muscle contraction, the cardiac action potential, hormonal and neurotransmitter secretion, cell division and repair, immune function, enzyme activity, membrane structure and blood coagulation. Thus, the maintenance of Ca supply and the control of its regulation are vital concerns to those caring for critically ill patients. This manuscript details information regarding the assessment of the circulating Ca level, causes for hypocalcemia and hypercalcemia and the treatment of Ca abnormalities in the critically ill patient.

Measurement of Blood Calcium

Ca circulates in the blood in three forms: an ionized and physiologically active form, a protein-bound form and a chelated form. Most clinical laboratories measure the total serum Ca rather than the ionized form. However, alterations in the amount of protein present, the percentage of Ca which is bound to protein and the amount of Ca

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which is chelated may affect the clinical relevance of the total serum Ca measurement [16].

Protein-bound Ca (primarily albumin) accounts for about 40% of the total circulating Ca [16–18]. Thus, alterations in serum albumin, which are commonly encountered in critically ill patients (albumin frequently varies from 1.0 to 5.0 g/dl), can change the total serum Ca concentration by as much as 30%. The percentage of Ca which is protein-bound is variable, and we have found that it ranges from 30 to 50% in critically ill patients. The total amount of Ca bound to albumin can range from 0.5 to 1.5 mg per gram of albumin. A variety of factors influence the Ca binding capability of the albumin molecule. Blood pH alters Ca binding; acute acidosis decreases protein binding, while acute alkalosis increases protein binding. A measurement of the total serum Ca concentration in critically ill patients with acid-base disorders may therefore give deceiving results. For example, a patient hyperventilated for the control of elevated intracranial pressure may develop ionized hypocalcemia, without abnormalities in the total serum Ca concentration, due to an alkalosis-induced increase in Ca binding to proteins. Patients given sodium bicarbonate for the control of a metabolic acidosis may also develop acute ionized hypocalcemia.

Free fatty acids (FFAs) constitute a major metabolic fuel for the body and are carried in the circulation bound to the albumin molecule [23]. FFAs increase Ca binding to albumin [1, 23] and may form a portion of the Ca binding site. Serum FFA levels increase during critical illness due to illness-induced elevations in plasma levels of epinephrine, glucagon, growth hormone and corticotropin, as well as decreases in serum insulin action.

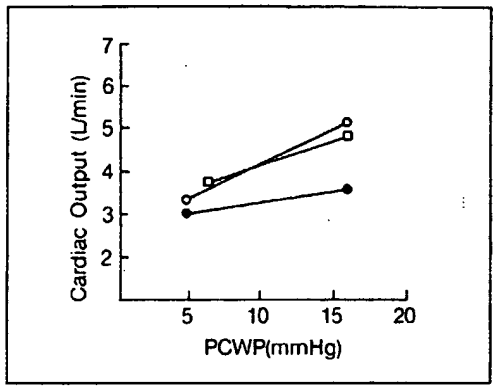

Fig. 1. Cardiac output versus pulmonary capillary wedge pressure (PCWP) in patients following volume loading with saline (□; n = 6), albumin (●; n = 6) or calcium-albumin solutions (○; n = 6).

Elevations in FFA levels, sufficient to alter Ca binding, may also occur after the administration of heparin sodium, intravenous lipids, epinephrine, norepinephrine, isoproterenol or alcohol. These pharmacologic agents are commonly used in critically ill patients. Increases in serum FFA concentrations in acutely ill and stressed patients may alter the distribution of Ca between bound and free states and may modulate free Ca levels in pathologic states.

Changes in the concentration of chelating substances (e.g. phosphate, bicarbonate, albumin, citrate, radiocontrast dye) may also lower the circulating ionized Ca level [16, 17]. Citrate is used as a blood preservative and anticoagulant, while albumin is commonly used to replenish intravascular volume during volume resuscitation. Resuscitation of patients with albumin alone is associated with less of an increase in cardiac contractility than when albumin is supplemented with Ca or when saline is used (fig. 1). Albumin causes a decrease in the

Table 1. Detection of ionized hypocalcemia and hypercalcemia

	Hypocalcemia		Hypercalcemia	
	Ca_t	Ca_c	Ca_t	Ca_c
Sensitivity, %	95	89	38	15
Specificity, %	32	46	100	100
Predictive power of positive test, %	16	6	100	100
Predictive power of negative test, %	98	97	95	93

Ca_t = Total calcium; Ca_c = calculated ionized calcium.

serum level of ionized Ca, while the other two modes of therapy do not. Citrate-induced decreases in ionized Ca are usually transient and without hemodynamic effect [17]. Decreases in ionized Ca values during blood transfusion correlate with elevations in circulating citrate levels and speed of transfusion. Denlinger et al. [8] administered citrated blood to anesthetized adult patients at rates of 50, 100 and 150 ml/min and found transient decreases in ionized Ca levels of 14, 31, and 41%, respectively. The metabolism of citrate is affected by tissue perfusion, body temperature, acid-base status and the activity of rate-limiting enzymes in the liver and kidneys. When transfusion rates exceed citrate metabolism, citrate levels rise and ionized Ca values fall. Clinically, citrate clearance is decreased in patients with hypothermia, impaired hepatic function or renal insufficiency. The hypocalcemic effect of citrate is accentuated in patients with impairment of the parathyroid-vitamin-D axis and in patients with cardiac insufficiency.

Many attempts have been made to mathematically correct the total serum Ca concentration for alterations in circulating albumin levels and arterial pH. Despite these attempts, total serum calcium and calculated ionized Ca levels are poor predictors of the physiologically active ionized Ca fraction [20]. Although they have a high sensitivity, total serum and calculated values of ionized Ca lack specificity and positive predictive power for detecting ionized hypocalcemia (table 1). However, since most forces lower the levels of total serum Ca and calculated ionized Ca during critical illness, these measurements have high specificity but low sensitivity for detecting ionized hypercalcemia. We believe that the discrepancy between measurements results from the contribution of other factors (e.g. FFA) to Ca binding. These factors vary between patients and, thus, the ionized Ca remains the only good clinical method for accurately assessing circulating Ca status during critical illness.

Causes of Hypocalcemia

Hypocalcemia is common in the critically ill patient, and its incidence (15–40%) depends largely upon the diseases encountered (e.g. sepsis, pancreatitis) and the underlying status of the patients (e.g nutritionally depleted, renal insufficiency). Most hypocal-

	Hypercalcemia	
	Ca_t	Ca_c
	38	15
	100	100
	100	100
	95	93

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cemic patients have an impaired ability to mobilize Ca under the stress of critical illness due to defects within the parathyroid-vitamin-D axis. The most common causes of hypocalcemia [16] are sepsis, magnesium depletion, neck surgery, dietary vitamin D deficiency, renal failure and the exogenous administration of hypocalcemic agents (e.g. chelators and drugs which decrease bone turnover; table 2).

The hypocalcemia occurring in patients with sepsis has multiple etiologies [19]. Some patients have dietary vitamin D deficiency, while others have acquired parathyroid gland insufficiency, renal 1-hydroxylase insufficiency or peripheral resistance to calcitriol [19]. Renal 1-hydroxylase deficiency usually occurs when renal insufficiency accompanies sepsis. Animal studies suggest that in vivo endotoxin can induce hypocalcemia and impair Ca mobilization [22]. At present, we feel that toxic substances are released into the circulation during sepsis and that these substances impair the activation of the parathyroid-vitamin-D-skeletal axis. Hypocalcemia occuring in patients with pancreatitis may have similar etiologies [18].

Table 2. Causes of hypocalcemia

Sepsis
Magnesium deficiency or excess
Neck surgery (secondary hypoparathyroidism)
Vitamin D deficiency
Dietary
Renal hydroxylase deficiency
Chelation
Phosphate
Blood
Albumin
Pancreatitis
Hungry-bone syndrome
Toxic-shock syndrome
Drugs (e.g. calcitonin)
EDTA
Ethylene glycol
Aminoglycosides
Cis-platinum
Mithramycin
Protamine
Sodium fluoride

Magnesium abnormalities are common in critically ill patients and may cause hypocalcemia [2, 6, 12, 15]. Severe hypomagnesemia and hypermagnesemia both inhibit parathyroid hormone (PTH) secretion. Hypomagnesemia may also impair PTH action at its receptor and cause vitamin D resistance. Since magnesium is an important cofactor for the activation of adenylate cyclase, it is possible that severe deficiency leads to an impairment of the adenylate cyclase system and deranged PTH release and skeletal resistance. Hypomagnesemia is seen clinically as a result of malnutrition, decreased gut magnesium absorption and/or excessive stool losses, and impaired renal magnesium conservation. Medications which disrupt the ability of the renal tubules to reabsorb magnesium include diuretics, aminoglycosides, amphotericin B, cis-platinum, cardiac glycosides and calcium. Aminoglycosides have been reported to cause hypomagnesemia in 38% of patients and hypocalcemia in 10% [21]. Hypomagnesemic hypocalcemia responds poorly to Ca therapy alone but does respond to magnesium repletion.

Hypocalcemia may occur when surgery involves removal of a parathyroid adenoma, total or near-total thyroidectomy, or bilateral neck surgery for cancer. Hypocalcemia is usually transient (lasting a few days). Parathyroid insufficiency may result from glandular suppression following removal of an adenoma, interference with parathyroid

blood supply or intraoperative release of calcitonin. Hypocalcemia may also result from excess bone mineralization (hungry-bone syndrome) when high levels of PTH or thyroid hormone are acutely lowered.

Vitamin D deficiency is being increasingly recognized as an important cause of hypocalcemia in the intensive-care unit. Many patients are chronically ill, malnourished, and have minimal sunlight exposure. They have low serum calcifidiol levels, suggestive of dietary vitamin D deficiency. Other patients have renal insufficiency with a deficiency of the renal 1-hydroxylase system responsible for the production of calcitriol. These patients frequently have normal Ca levels as outpatients but have an impaired ability to mobilize Ca during the hypocalcemic stress of critical illness. Patients with renal failure are also vulnerable to the hypocalcemic effects of dialysis. Maynard et al. [14] showed that the drop in blood pressure induced by hemodialysis was reduced when a high Ca dialysate was used. Henrich et al. [11] demonstrated that ionized Ca values during dialysis were key factors affecting left ventricular contractility.

Hyperphosphatemia may cause hypocalcemia as a result of Ca precipitation, inhibition of bone resorption and suppression of renal 1-hydroxylation of vitamin D [5]. The most common causes for this syndrome in the intensive-care unit are exogenous phosphorus administration, tumor lysis syndromes following chemotherapy, renal failure and rhabdomyolysis. Other chelating substances (e.g. albumin, citrate, radiocontrast dye, EDTA, protamine) may also cause hypocalcemia. In addition, hypocalcemia may be caused by drugs which decrease bone Ca resorption (e.g. calcitonin, mithramycin, fluoride; table 2).

Clinical Features and Therapy f Hypocalcemia

Mild to moderate ionized hypocalcemia (Ca = 3–4 mg/dl; normal 4–5 mg/dl) is usually well tolerated in the critically ill patient. However, the threshold for the development of hypocalcemic symptoms is not well defined. Over the past 2 years we have seen 6 patients who had cardiac arrests from hypocalcemia. These patients all had serum values of ionized Ca below 2.5 mg/dl, and most had another electrolyte (e.g. K^+, Mg^{2+}) abnormality as well. A review of the literature revealed that cardiac arrest from hypocalcemia was virtually always associated with an ionized Ca level less than 2.5 mg/dl. In addition, isolated animal hearts frequently arrest at ionized Ca levels of 2.0 mg/dl. Thus, it appears that cardiac arrest is common when the ionized Ca level approaches 2.5 mg/dl, and we recommend treating all patients whose ionized Ca concentration is below 3.0 mg/dl.

Hypocalcemia may present with a variety of signs and symptoms that relate primarily to increased neuronal irritability and cardiovascular insufficiency [16]. Cardiovascular manifestations are the most common clinical features of hypocalcemia seen in critically ill patients. Patients may develop hypotension, decreased cardiac contractility, arrhythmias and drug resistance. Hypocalcemia should always be considered in patients with hypotension that responds poorly to fluids or to pressor agents. Restoration of a normal circulating Ca level may restore vascular tone and improve cardiac contractility. In other studies [4], we have shown that hypocalcemia impairs the chronotropic effects of glucagon, and Chopra et al. [7] have shown that hypocalcemia impairs digi-

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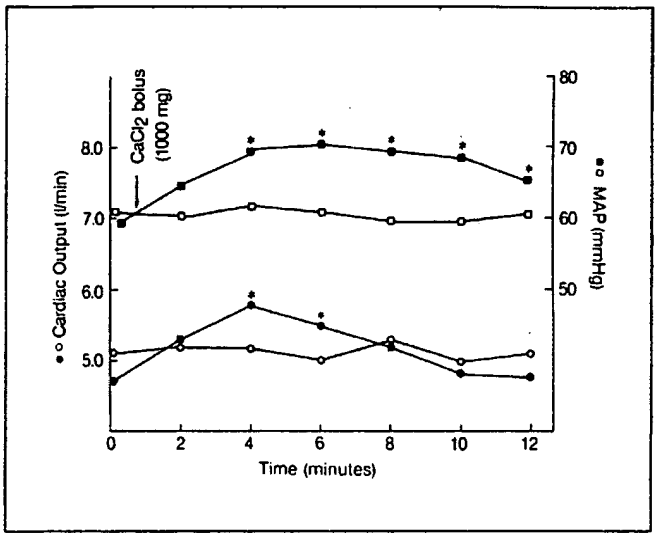

Fig. 2. Cardiac output and mean arterial pressure (MAP) responses to calcium chloride (1,000 mg i.v.) in hypocalcemic (●, ■; n = 6) and normocalcemic (○, □; n = 6) patients. * $p < 0.05$ compared to baseline.

talis action. Thus, many drugs appear to be dependent on circulating Ca for their maximal effects. Ca may also be an effective inotropic drug in patients with advanced cardiac disease who have β-adrenergic receptor down-regulation as a result of chronic sympathetic stimulation [10]. These data suggest that hypocalcemic patients with cardiovascular compromise may benefit from Ca administration. Animal studies [9] show that animals with hypocalcemia respond to Ca administration by increasing cardiac output and blood pressure. The net result is an increase in oxygen delivery to the tissues. On the other hand, when Ca is given to normocalcemic animals, the predominant effects are an increase in systemic vascular resistance and blood pressure. Cardiac output may remain unchanged or decrease. A decrease in cardiac output may cause a decrease in oxygen delivery. We have found similar results from Ca during its administration to patients with hypotension (fig. 2). These results add further importance to ionized Ca measurement prior to Ca administration so as to avoid undesirable decreases in tissue perfusion.

Although less common, hypocalcemia may also present with laryngospasm, paraesthesias, tetany, seizures, weakness, dementia and psychosis [16].

Causes of Hypercalcemia

Hypercalcemia is not as common (3–5%) as hypocalcemia in critically ill patients. The most common causes of hypercalcemia seen in the intensive-care unit are malignancy, hyperparathyroidism, and posthypocalcemic hypercalcemia, although many other causes exist (table 3). The reader is referred elsewhere for a more complete discussion of the many causes of hypercalcemia [3, 16, 18].

Hypercalcemia occurs in 10–20% of patients with malignancy as a result of a direct

tumor osteolysis of bone and from the secretion of humoral substances which stimulate bone resorption. Humeral bone resorbing substances include 'PTH-like' substances, calcitriol, osteoclast-activating factor and prostaglandins. 'PTH-like' substances cross-react with PTH in the radioimmunoassay for PTH but are not identical to PTH. They are felt to be responsible for most instances of humoral hypercalcemia of malignancy and most likely represent a heterogeneous group of molecules. Hypercalcemia in patients with malignancy is aggravated by many of the factors which occur in critically ill patients. Some of these include dehydration, immobilization and renal insufficiency or failure.

Primary hyperparathyroidism occurs in the general population with a prevalence that ranges from 0.03 to 0.1%. When these patients seek medical assistance, many for unrelated causes, their hypercalcemia is recognized. Hypercalcemia is aggravated by dehydration, immobilization and renal insufficiency or failure.

Transient hypercalcemia is occasionally seen in patients following a period of hypocalcemia (fig. 3). These patients develop hypocalcemia for a variety of reasons. When one measures PTH levels they are elevated. Following recovery from the hypocalcemia, there is a period of rebound hypercalcemia associated with elevated PTH concentrations. This posthypocalcemic hypercalcemia probably results from parathyroid hyperplasia which develops during the period of hypocalcemia. This situation is analogous to secondary hyperparathyroidism which develops in patients with renal failure. With recovery, both PTH and calcium levels return to normal. Patients frequently require Ca supplements during the hypocalcemic phase but require Ca restriction during the hypercalcemic phase.

Immobilization rarely causes significant hypercalcemia in patients with normal bone turnover. However, significant hypercalcemia may develop during bed rest in patients with rapid bone turnover (e.g. children, postfracture patients, patients with malignancy or hyperparathyroidism, patients with Paget's disease of the bone). Serum PTH and calcitriol levels are suppressed unless the etiology is from hyperparathyroidism.

Granulomatous diseases may cause hypercalcemia. Although sarcoidosis is the most frequent cause, hypercalcemia has also been reported in patients with tuberculosis and fungal granulomatous processes. Hypercalcemia appears to result from excess calcitriol synthesis by lymphocytes in the granulomata.

Clinical Features and Treatment of Hypercalcemia

Most patients with mild degrees of hypercalcemia are asymptomatic. However, severe hypercalcemia may cause life-threatening problems (table 4) [16]. The most common clinical features include nephrocalcinosis, free water wasting ('nephrogenic diabetes insipidus'), anorexia, constipation, weakness and impaired mentation. Life-threatening problems may develop acutely and include cardiac arrhythmias, digitalis sensitivity, coma, seizures and renal failure. We have shown that hypercalcemia diminishes the hypertensive effects of epinephrine. Catecholamine action may be inhibited via feedback inhibition of Ca on adenyl cyclase and/or inositol phospholipid turnover. The

Fig. 3. Posthyp
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Table 3. Causes

Malignancy
Hyperparathyroidi
Posthypocalcemic
Iatrogenic calcium
Immobilization
Renal causes
Chronic renal f
Recovery from
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Granulomatous dis
Hyperthyroidism
Phosphorus depleti
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Drugs
Calcium
Estrogens or pr
Lithium
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Theophylline
Thiazides
Vitamin D or A

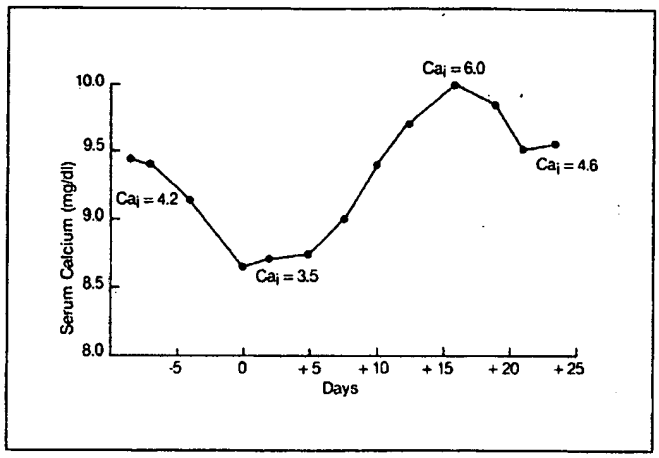

Fig. 3. Posthypocalcemic hypercalcemia in a group (n = 6) of critically ill patients. Ca_i = Ionized calcium (mg/dl).

Table 3. Causes of hypercalcemia

Malignancy
Hyperparathyroidism
Posthypocalcemic hypercalcemia
Iatrogenic calcium administration
Immobilization
Renal causes
Chronic renal failure
Recovery from acute renal failure
After renal transplantation
Granulomatous disease
Hyperthyroidism
Phosphorus depletion syndrome
Hypocalciuric hypercalcemias
Drugs
Calcium
Estrogens or progestins for malignancy
Lithium
Milk-alkali syndrome
Theophylline
Thiazides
Vitamin D or A

Table 4. Clinical features of hypercalcemia

Cardiovascular
Hypertension
Arrhythmias
Digitalis sensitivity
Catecholamine resistance
Urinary system
Nephrocalcinosis
Nephrolithiasis
Tubular dysfunction
Renal failure
Gastrointestinal
Anorexia
Nausea/vomiting
Constipation
Peptic ulcer
Pancreatitis
Neuromuscular
Weakness
Neuropsychiatric
Depression
Dementia
Disorientation
Psychosis
Obtundation
Coma
Seizures

threshold for the development of symptoms is variable. Factors such as the rapidity with which the Ca rises, accompanying renal failure, electrolyte disturbances, cardiovascular status and the general state of debilitation of the patient may alter the threshold.

Definitive treatment for hypercalcemia lies in the correction of the cause; however, frequently a definitive procedure cannot be performed (e.g. surgery) due to the underlying debilitated state of the patient. In addition, it may be necessary to treat patients acutely due to symptoms and complications. Therapy is aimed at minimizing Ca entry and maximizing Ca exit from the circulation [16]. General measures of treatment include hydration, correction of electrolyte abnormalities, removal of offending drugs, dietary Ca restriction and mobilization of the patient. Renal Ca excretion is increased with saline, furosemide and dialysis. Bone resorption can be decreased with calcitonin, mithramycin, glucocorticoids, indomethacin, diphosphonates, cis-platinum or gallium nitrate. Ca levels may be acutely lowered with chelators such as phosphate, EDTA, sodium citrate or sodium sulfate. WR-2721, a parathyroid gland inhibitor, has also been used clinically in a small number of patients. The effects of Ca on the cardiovascular system may be antagonized with Ca channel blockers such as verapamil and nifedipine.

Calcium and Ischemia

Calcium has recently been removed from the Standards and Guidelines for Cardiopulmonary Resuscitation based upon its harmful effects during ischemia and shock [13]. Studies suggest that Ca may be toxic to cells during low perfusion states and that Ca channel blockers may be beneficial [13].

In shock or other ischemic disorders, cellular Ca homeostasis is disrupted, and Ca accumulates within the cell. This accumulation of cytosolic Ca may be due to either an increase in cell membrane permeability and/or a decreased activity of the cellular pumps or cellular organelles which sequester Ca or remove it from the cell. An uncontrolled rise in cytosolic Ca can initiate a number of intracellular processes which include excitation-contraction coupling, endo- and exocytosis, and enzyme activation. These processes may exacerbate the hemodynamic and metabolic insufficiency underlying ischemic and shock states. For example, smooth muscle constriction in blood vessels (vasoconstriction) may produce or worsen ischemia by decreasing nutrient blood flow to cells and tissues. Phospholipase activation by Ca can produce membrane damage and liberate FFAs, which stimulate the production of superoxide and hydroxyl radicals and increase the production of eicosanoids. These toxic products may cause further cellular damage. Elevation in cytosolic Ca may also activate proteases, nucleases, Ca-dependent ATPases and uncouple oxidative phosphorylation. For example, protease activation converts xanthine dehydrogenases to xanthine oxidases. Xanthine oxidases react with oxygen and hypoxanthine to produce superoxides and oxygen-free radicals. Thus, although Ca is essential for cellular function, uncontrolled increases in intracellular Ca may also damage the cell.

It is important to point out that it is unclear whether the alterations in Ca fluxes leading to intracellular Ca overload are a cause for the cellular metabolic derange-

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ments in shock and ischemia or whether these changes are a result of other pathophysiological processes which occur. In either case, the administration of agents which block Ca entry into cells or block Ca action may help prevent cellular injury and maintain organ function.

Ca channel blockers have been used extensively and successfully in the treatment of myocardial ischemia and cerebral ischemia [13]. Experimental data also suggest that these agents are useful in preserving cellular integrity during hemorrhagic and septic shock. We have shown that Ca administration increases mortality during endotoxin administration, while EGTA (a Ca chelator) and verapamil improve survival. The manipulation of circulating Ca levels and the blockade of Ca entry into cells are an important area for further research in ischemia and shock.

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